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SUMMARY OF THE PHD THESIS

THE EFFECTIVENESS OF THE CARDIOVASCULAR PREVENTION STRATEGY IN THE COMPLEX MANAGEMENT OF DYSLIPIDEMIA

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T i m i s o a r a

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1. INTRODUCTION: DYSLIPIDEMIA, ACTUAL CONTEXT, FOCUS ON FAMILIAL HYPERCHOLESTEROLEMIA

The cardiovascular diseases are a significant cause for mortality all over the world; they account for 45% of all deaths in Europe. They also cause an important loss in DALY (11% DALY loss in women and 14% DALY loss in men, respectively). Experiments as the one in North Karelia showed that the vast majority of cardiovascular events are preventable by population control of all modifiable cardiovascular risk factors. Out of all cardiovascular risk factors, dyslipidemia plays a vital part in cardiovascular prevention due to its high prevalence among adults and children alike. The consequences of dyslipidemia have a wide clinical spectrum.

Data suggest that 33% of all cases of coronary artery disease are directly linked to the serum cholesterol levels. Although nowadays there is a wide range of lipid-modifying treatments, their effectiveness is quite low. Overall, approximately a quarter of all treated patients reach their LDL cholesterol goal. In 2018, an observational study regarding dyslipidemia management in high and very high cardiovascular risk patients took place in Central and Eastern Europe and Israel. In this study, Romania had the highest number of patients enrolled. The results of this study were disappointing showing that less than a quarter of high risk patients (23.8%) and less than half of very high risk patients (42%) reached their LDL cholesterol treatment target.

Due to these facts, the necessity of a local study regarding the current management of dyslipidemia in Timisoara appeared. This was an observational retrospective study, which enrolled consecutive patients with dyslipidemia from Cardioprevent Foundation ambulatory clinic. The main objective of the study was to estimate the proportion of patients reaching the LDL cholesterol target levels defined by 2016 ESC. Chapter 3 of the special part of this paper describes the methods and the results of this study.

Familial hypercholesterolemia differs from polygenic dyslipidemia by several characteristics as it follows:

- It is an autosomal dominant monogenic disorder. This means that if one parent has heterozygous familial hypercholesterolemia, the chances for each child of inheriting the disease are 50%. This fact results in a high prevalence of the disease. 30-40 years ago it was considered that heterozygous familial hypercholesterolemia affected 1 in 500 persons. Many

epidemiologic studies confirm that the prevalence of this disease is at least double, affecting 1 in 200-300 persons.

- The levels of LDL cholesterol are genetically determined.
- High levels of LDL cholesterol are present since birth. Thus even young persons with familial hypercholesterolemia have a long exposure time to this risk factor. This fact gives to familial hypercholesterolemia patients a high cardiovascular risk. The first acute cardiovascular event (myocardial infarction) appears in these patients at about 35 years of age.
- The disease is symptom-free until complications occur (symptomatic early atherosclerotic disease) making early diagnosis difficult. Early diagnosis is based on screening strategies. Most of the countries report diagnosis rates of maximum 5%.
- There aren't any universally accepted diagnostic criteria. Three diagnostic scores are frequently used: DCLNC, Simon-Broome criteria, and MedPed criteria.
- Early diagnosis is of utmost importance because it is effective in preventing atherosclerotic disease and acute cardiovascular events.
- Due to very high levels of LDL cholesterol (usually over 200 mg/dl) the treatment should be able to lower the LDL cholesterol levels by more than 50%. Thus in these patients the administration of potent statins (such as atorvastatin or rosuvastatin) is preferred. It is more likely that these patients need combined lipid-modifying medication (statins+ cholesterol absorption inhibitors+ PCSK9 inhibitors).
- Genetic characteristics (such as the low number of hepatic LDL cholesterol receptors) contribute to standard lipid-modifying treatment resistance.

Unfortunately, at the present in Romania there are no data on the prevalence of familial hypercholesterolemia, although cases of 35-year-old men having myocardial infarction are quite frequent. That is the reason why I decided to conduct an epidemiologic study with the main objective of estimating the prevalence of familial hypercholesterolemia in Romania. This study can be used as a starting point for further population screening for familial hypercholesterolemia. Chapters 1 and 2 of the special part of this paper describe the methods and results of our two studies aiming to discover the prevalence of familial hypercholesterolemia in adults and teenagers from Timisoara, respectively.

These tree studies will be briefly presented below (their objectives, methods, results, and scientific importance).

2. PRELIMINARY DATA ON FAMILIAL HYPERCHOLESTEROLEMIA PATIENTS FROM ROMANIA

The main objective of this study was to find the prevalence of familial hypercholesterolemia in Timisoara. The secondary objectives were the study of the clinical and metabolic characteristics of these patients (their LDL cholesterol levels, their personal and familial history in relation with hypercholesterolemia, the presence of coronary/ cerebral/ peripheral artery disease).

I have conducted an epidemiological retrospective study between January 2015 and January 2018 among consecutive patients admitted to the ambulatory practice, for a cardiology consultation. Data were collected from the ICMed electronic database, including, age, gender, laboratory test results (LDL cholesterol levels), recorded history of CAD or peripheral vascular disease (premature cerebrovascular atherosclerosis or peripheral arteriopathy), and prescription of statin medication. The majority of the enrolled patients were not on statin therapy at the time of enrollment and, for those who were, I calculated their baseline LDL cholesterol levels by multiplying their current LDLc levels by 1.43. Using the information from the patient records, I have calculated the DCLN score, which included assessment of LDL cholesterol concentrations, clinical characteristics such as peripheral vascular disease and premature CAD, presence or absence of tendon xanthoma or arcus cornealis, and a family history of premature heart disease. The enrollment criteria in this study were FH score over 3 points indicating at least a possible FH diagnosis. Out of 8329 patients examined between January 2015 and January 2018, I have enrolled 59 patients in this study.

The results of this study were similar to the results from other international studies. From this study, the conclusion was that the prevalence of familial hypercholesterolemia in the adult population from Romania was 0.46% (1 in 213 patients). 91.52% of the patients had a DCLNC score of possible familial hypercholesterolemia, while 6.7% of the patients had a score of probable familial hypercholesterolemia and 1.6% of the patients had a score of certain familial hypercholesterolemia. The mean age of patients was 54.9 years. 8.4% of the patients had a first degree relative with premature coronary artery disease, while 5% of the patients had a relative with hypercholesterolemia (LDL cholesterol> 190 mg/dl). 10.16% of the patients had personal history of coronary artery disease and 15.25% of the patients

had peripheral arterial disease (out of which 6.7% had subclinical carotid atherosclerosis). The medium LDL cholesterol levels upon enrolment was 229.84 mg/dl for the untreated patients.

Familial hypercholesterolemia is a dominant autosomal genetic disease representing the most frequent monogenic disorder of the cholesterol metabolism. This disease exposes patients to very high levels of LDL cholesterol since birth, thus given them a particularly high cardiovascular risk. The main complication of the disease is premature cardiovascular disease. Familial hypercholesterolemia diagnosis results in a dramatic 100-fold increase in coronary mortality in young people (aged 20-40 years). The mean age of myocardial infarction is 35 years in heterozygous familial hypercholesterolemia patients.

The results of this study are consistent with findings from other epidemiologic studies from around the world: 1 in 213 patients had a DCLNC score of minimum 3 points, corresponding to possible FH. Although the familial hypercholesterolemia prevalence varies among studies due study design, different diagnostic criteria used and the studied population, most commonly the reported prevalence is about 1 in 200-300 persons.

Until now, data about dyslipidemia prevalence in Romania are rather scarce and basically I had no data at all on the familial hypercholesterolemia patients. This study is the first of its kind in Romania aiming to find the prevalence of FH in a primary healthcare prevention practice.

This study is important as it can represent a starting point in population screening for the disease. This stage is important for early diagnosis and effective primary prevention. Based on this study, in this chapter of the thesis I presented a diagnosis algorithm for familial hypercholesterolemia starting form primary healthcare practice. This algorithm is at the same time cheap, easy to apply and effective in uncovering familial hypercholesterolemia cases.

3. PROJECT ON FINDING THE PREVALENCE OF FAMILIAL HYPERCHOLESTEROLEMIA IN TEENAGERS FROM TIMISOARA

Based on the same idea as the previous study from this paper and willing to extend its results, I have conducted an epidemiologic study on teenagers from Timisoara, having as main objective the evaluation of familial hypercholesterolemia prevalence in teenagers (aged 10-11 years).

This epidemiologic study took place in the schools from Timisoara, and involved 4th grade students. Seven schools took part in the study. Previous to enrollment, I conducted an information campaign about familial hypercholesterolemia. In group meetings, I discussed themes as the genetic character of this disease, the main signs and symptoms of the disease, the cardiovascular risk of familial hypercholesterolemia patients, as well as the importance of screening for early diagnosis and prevention, and treatment options. All parents received informative brochures on the disease. After the parents signed an informed consent, I analyzed a peripheral blood sample from the children and performed a lipid profile with a point of care analyzer. I wrote the results on paper of different color. as it follows: the children received the results written on white paper if their lipid profile was normal and there was no suspicion of familial hypercholesterolemia; they received the results written on grey paper if they had borderline high LDL cholesterol raising a suspicion for familial hypercholesterolemia; they received the results written on red paper if they had extremely elevated LDL cholesterol raising a strong suspicion for familial hypercholesterolemia. Afterwards, the children with grey and red pieces of paper had the possibility to have a detailed lipid profile done for free by the Synevo Laboratories.

318 children were enrolled in the study, out of which 242 children (76.1%) had a normal lipid profile, 8 children (2.52%) had hypertriglyceridemia, 56 children (17.61%) had an LDL cholesterol level between 130-160 mg/dl, and 12 children (3.77%) had an LDL cholesterol level above 160 mg/dl. Two children (0.63%) had an LDL cholesterol level higher than 190 mg/dl, showing a very high probability for familial hypercholesterolemia.

This study had a very simple design. It was based on the results of other international studies which proved that under the age of 14, LDL cholesterol levels offer good discrimination between familial hypercholesterolemia and polygenic dyslipidemia.

The results of this study are worrisome; approximatively 25% of the enrolled children had dyslipidemia and the prevalence of familial hypercholesterolemia was 1 in 159 teenagers from Timisoara.

As far as I know, this was the first study from Romania aiming to discover the prevalence of familial hypercholesterolemia in teenagers from this country. The results of this study suggest that the evaluation of the lipid profile should be a routine event in children, offering the possibility for early diagnosis and effective primary prevention.

4. OBSERVATIONAL STUDY ON DYSLIPIDEMIA MANAGEMENT IN PATIENTS FROM TIMISOARA

The main objective of this study was to estimate the proportion of patients reaching the LDL cholesterol target set by 2016 ESC, with optimal lipid-modifying treatment. The secondary objectives of the study were the study of cardiovascular risk factors in the patients enrolled as well as the study of treatment strategies applied for reaching the LDL cholesterol target (type of lipid-modifying medication, dosage of lipid modifying medication, and treatment changes in time).

The study was an observational epidemiologic retrospective study. It took place in Timisoara during January 1, 208 - December 21, 2019. Out of 2563 patients evaluated in the Cradioprevent Foundation ambulatory clinic during that year, I enrolled all consecutive 415 patients who had a lipid profile result issued in 2018. Out of all patients, 195 patients (46.98%) had obesity, 42 patients (10.36%) were smokers and 120 patients (30.12%) had type 2 diabetes. As far as the number of major modifiable risk factors associated to dyslipidemia, 169 patients (47.07%) associated a single risk factor, 75 patients (20.89%) associated two risk factors, and only 3 patients (0.83%) associated three risk factors. A number of 112 patients (31.19%) did not have any other risk factors associated to dyslipidemia. The most frequent association was obesity and diabetes, which were present in 54 patients (15.04%). A total of 48 patients (11.56%) had cardiovascular atherosclerotic disease in different sites: 37 patients (8.91%) had coronary artery disease, 13 patients (3.13%) had carotid artery disease, 4 patients (0.96%) had renal artery stenosis and 6 patients (1.44%) had peripheral artery disease. Regarding the number of affected vascular territories, the distribution was: 39 patients (81.25% of the patients with cardiovascular atherosclerotic disease) had only one vascular territory affected, 5 patients (10.41% of the patients with cardiovascular atherosclerotic disease) had two affected vascular territories, and 4 patients (8.33% of the patients with cardiovascular atherosclerotic disease) had three affected vascular territories. In over 90% of the patients enrolled in the study the lipid-modifying treatment was started with statin in monotherapy. The most frequently used statins were atorvastatin (in 32.47% of the patients) and rosuvastatin (in 64.65% of the patients). In 77.29% of the patients, the statin treatment was of medium intensity and in 22.7% of the patients the statin treatment was of high intensity.

122 patients had a LDL cholesterol measurement previous to enrollment. The LDL cholesterol values and medication of these patients were recorded retrospectively. All these patients had either high cardiovascular risk or very high cardiovascular risk. Under optimal lipid-modifying treatment, the mean LDL cholesterol levels were 26.1% lower in the high cardiovascular risk patients and 22.7% lower in the very high cardiovascular risk patients. 44% of the high cardiovascular risk patients and 27.8% of the very high cardiovascular risk patients reached the LDL cholesterol goal. In the vast majority of patients, lipid-modifying treatment remained unchanged during the follow-up period (52% of high cardiovascular risk patients and 63.91% of very high cardiovascular risk patients). The most frequent change in the lipid-modifying treatment was doubling the statin doze (in 12% of high cardiovascular risk patients and in 18.55% of very high cardiovascular risk patients) followed by the adding of ezetimibe to statin therapy (in 8% of high cardiovascular risk patients and in 7.21% of very high cardiovascular risk patients). Both treatment strategies had the same effectiveness. As a consequence of doubling the statin dose, the LDL cholesterol levels dropped by 30.12% and as a consequence of adding ezetimibe to statin treatment, the LDL cholesterol levels dropped by 30.43%.

The factors that significantly influenced treatment effectiveness were: initiation of statin treatment ($p=0.001$); dosage of statin ($p=0.004$) and adding ezetimibe to statin treatment ($p=0.002$). All the other parameters (age, sex category, BMI, smoking status, presence of diabetes, level of HDL cholesterol, level of triglycerides, presence of chronic kidney disease, and presence of atherosclerotic disease) did not significantly influence the treatment effectiveness.

Multiple international studies showed that despite optimal medication, only a minority of patients reached their LDL cholesterol goal. This study provides a snapshot of the clinical and metabolic characteristics of the patients in my cardiology ambulatory clinic and of the most used lipid-modifying treatments. This study confirms the low percentage of patients reaching their LDL cholesterol goal, suggesting that there is still place for better management of these patients.

5. CONCLUSIONS

The purpose of this paper was to establish the prevalence of familial hypercholesterolemia in Timisoara as well as to analyze the lipid-modifiable medications used in patients with dyslipidemia.

The conclusion of the first study is that the prevalence of familial hypercholesterolemia in adults from Timisoara is 1 in 213 persons, similar to its prevalence in other countries

From the second study, the conclusion was that the prevalence of familial hypercholesterolemia in teenagers from Timisoara is 1 in 159 children, slightly higher than the one reported in adults.

The third study showed that

- The most frequently used initial treatment for dyslipidemia is statins.
- The preferred statins are atorvastatin and rosuvastatin.
- The most frequent change in treatment was doubling the statin dose followed by adding ezetimibe to statin treatment.
- Both treatment strategies had the same effectiveness (they lowered the LDL cholesterol levels by 22-35%).
- Initiation of statin treatment, the statin dose, adding ezetimibe to statin treatment significantly influenced the percentage of patients reaching their LDL cholesterol goal.
- Age, sex category, BMI, smoking status, presence of diabetes, level of HDL cholesterol, level of triglycerides, presence of chronic kidney disease, presence of atherosclerotic disease did not significantly influence the percentage of patients reaching their LDL cholesterol goal.
- The treatment lowered the LDl cholesterol levels by 25.2%.
- 27.8% of high cardiovascular risk patients and 44% of very high cardiovascular risk patients reached their LDL cholesterol targets.