UNIVERSITY OF MEDICINE AND PHARMACY

„CAROL DAVILA", BUCHAREST

DOCTORAL SCHOOL

GENERAL MEDICINE

Cost efficiency in clinical management of hypertension

ABSTRACT OF DOCTORAL THESIS

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PhD thesis abstract

Hypertension is a real major public health problem and a significant cause of death worldwide and its incidence is increasing, having been recognised as a major cardiovascular risk factor in the Framingham Heart Study (FHS), the first observational, cohort, prospective study dedicated to the epidemiology of cardiovascular disease.

By defining the concept of cardiovascular risk factors and identifying them, the Framingham study has laid the groundwork for the development of public health analyses and policies aimed at reducing the societal impact of cardiovascular disease.

Hypertension is a chronic condition and is generally associated with few or no symptoms. When symptoms do occur, this is usually when blood pressure reaches very high values, when it happens to rise suddenly and markedly enough to be considered a medical emergency.

The rare symptoms included on the list of hypertension are headaches, dizziness, nosebleeds, palpitations, but hypertension is largely asymptomatic, being is a „silent killer" that in most cases is not accompanied by symptoms.

Risk factors for hypertension can be classified into two broad categories: risk factors that cannot be modified and modifiable risk factors. The first category includes: age, race and heredity. Modifiable risk factors are behavioural and lifestyle factors. This category includes unhealthy eating habits, smoking, sedentary lifestyles, excessive alcohol consumption and obesity.

The quantification of the burden of a disease and therefore of hypertension is done by the DALY (disability adjusted life year) indicator. It represents one year of healthy life lost and sums the number of years of life lost due to premature death (YLL - years of life lost) with the number of years of life lived with disability of known severity and duration (YLD - years lived with disability of known severity and duration).

Quantification of mortality, morbidity and burden of hypertension by YLD presents a fragmented view of its impact on society. Added to this is the substantial economic burden resulting from direct medical costs related to prevention, diagnosis, treatment and follow-up of the hypertensive patient, management of acute and chronic complications due to poor adherence to treatment, as well as indirect costs due to loss of productivity through premature death or disability.

Today, hypertension has reached epidemic proportions. The proportion of the population with high blood pressure or hypertension has increased from 600 million in 1980

to almost 1 billion in 2008, to 1.39 billion in 2010, and is expected to rise to 1.56 billion in 2025 as a result of population growth and ageing.

According to World Health Organization estimates, globally for hypertension DALYs were 19,101,413 for both sexes, of which 8,864,898 in males and 10,236,515 in females. In the European Region, the DALY was 2,614,113 for both sexes, of which 1,167,611 for males and 1,446,525 for females.

AHA (American Heart Association) statistics from 2017 estimate that by the year 2030 direct costs related to cardiovascular disease will triple and indirect costs will increase by up to 58%. High blood pressure spending projections indicate $225 million per year in 2025 and an increase to $274 million in 2030.

The SEPHAR I, II, III (Study for the Evaluation of Prevalence of Hypertension and Cardiovascular Risk in Romania) series of studies has demonstrated improved awareness, treatment and control, and an increasing trend in the prevalence of hypertension at national level between 2005 and 2016.

All these data come in a context where global public health is undergoing a paradigm shift from „evidence-based medicine" (EBM) to „value-based medicine" (VBM).

Explicitly evaluating and quantifying, in economic terms, the use of resources allocated to the clinical management of hypertension is the first step towards achieving the goal of providing the best possible evidence-based, patient-preferred and, above all, cost-effective healthcare.

According to the latest Hypertension Management Guidelines developed by the European Society of Cardiology (ESC) together with the European Society of Hypertension (ESH), in line with the International Society of Hypertension (ISH) Guidelines, hypertension is conceptually defined as systolic blood pressure (SBP) ≥ 140mmHg and/or diastolic blood pressure (DBP) ≥ 90mmHg, in people aged 16 years and over, measured in the doctor's office. The values have been established following randomised clinical trials which have shown that from these thresholds onwards there are benefits of antihypertensive treatment and that the risk-benefit balance is in favour of the latter.

Out-of-office blood pressure determinations may prove to be a useful resource for screening and subsequent follow-up of hypertensive patients, with the potential to generate changes in the clinical management of hypertension, both in terms of increasing awareness and optimising therapeutic measures and increasing control of hypertension, both as a cardiovascular condition and as a cardiovascular risk factor.

Conceptual definitions of hypertension are subject to permanent change, depending on the results of ongoing clinical trials, and are relevant in terms of the actions or inactions they generate at public health policy level.

The prevalence of hypertension, as defined for values measured in the doctor's office, was estimated in 2015 at more than 1.1 billion people globally, including more than 150 million in Central and Eastern Europe. The global level of 1.5 billion is expected to be reached in 2025.

The latest country profile published by the European Commission in 2019 shows that cardiovascular disease and stroke remain the leading causes of death in Romania, responsible for more than 550 deaths per 100,000 inhabitants in 2016.

The death rate from cardiovascular disease, for which hypertension is the most important risk factor, is 256 per 100,000 inhabitants, more than 3 times higher than the European average of 80 per 100,000 inhabitants.

At national level, according to the SEPHAR III study, hypertension has a prevalence of 45.1%, ranging from 15.4% for the 18-24 age group to over 66% in respondents aged over 65.

About 1 in 5 hypertensive Romanians do not know they suffer from hypertension, and 7 out of 10 Romanians diagnosed with this „silent killer" do not have optimal control of the condition.

Taking into account the above mentioned aspects, in our PhD research we aimed to highlight the clinical management of hypertension and to highlight the need to integrate cost analysis when developing guidelines for the prevention, diagnosis and treatment scheme of hypertension, taking into account, the current profile of the patient with hypertension and factors such as opportunity cost, effectiveness, benefits and cost-effectiveness.

The general objectives of the present doctoral research are:

a)   analysis and dissemination of clinical management of hypertension, i.e. the need to integrate cost analysis when developing guidelines for the prevention, diagnosis and treatment of hypertension, also taking into account factors such as opportunity cost, effectiveness, benefits and cost-effectiveness.

b)   to highlight the current profile of the patient with hypertension, by studying vectors related to the study group regarding age, gender distribution, occupational status, associated conditions, BMI, salt intake, alcohol consumption, treatment compliance, cholesterol and LDLc values, smoking, sick leave days and sick retirement.

The formulation of the research hypothesis and objectives took into account some of the observations highlighted in both previous studies and guidelines, but adapted to the study base, but especially to the current global socio-economic climate that has led to a shift towards the concept of value called the „triple aim paradigm" (including distributive, technical and personal values).

In terms of the structure of the thesis, the opening part of the thesis contains the table of contents. The thesis consists of 3 chapters, divided into sections. At the end is the conclusion section. The thesis ends with an indication of the bibliography used.

In the general part of the doctoral thesis, hypertension, clinical management of hypertension and the costs associated with clinical management of hypertension have been addressed and synthetically highlighted, also considering factors such as opportunity cost, effectiveness, benefits and cost-effectiveness.

As for the special part of the doctoral thesis, in correlation with the proposed objectives, it was structured on 3 levels of analysis, namely study to outline the current profile of the patient with hypertension followed by outpatient services, study to outline the current profile of the patient with hypertension admitted to hospital and study on the impact of the COVID 19 pandemic on patients with hypertension.

For the study related to the current profile of the patient with hypertension, the selected group was represented by 721 patients registered with three family physicians in Galati County, with a diagnosis of primary hypertension.

The group of subjects of the study to outline the current profile of the patient with hypertension admitted to hospital was represented by 209 patients who were admitted between 2014 and 2019 in the clinical cardiology department of the County Emergency Hospital Sf. Ap. Andrei Galați, on which we retrospectively analyzed the observation sheets and data entered into the DRG system.

As regards the study on the impact of the COVID 19 pandemic on patients with hypertension, this was due to the restriction of freedom of movement as a result of the measures adopted to combat the Sars Cov 2 pandemic, which resulted in many patients with pre-existing conditions having restricted access or difficulties in accessing care. The study subject group consisted of 440 patients, representing in fact patients from Lot 1, who also agreed to respond to the specific questionnaire generated by the Sars Cov 2 pandemic.

Data collection for the research hypothesis and the objectives of the PhD thesis was carried out in the period 2018 - 2021, at the level of Galati County.

For the collection of research data, a direct process was used, through the direct involvement of the researcher in the process of collecting, processing and interpreting the data obtained from the study.

The material obtained in the data collection stage was statistically processed, following a thorough check to eliminate possible errors. 100% completed documents (questionnaires) were considered in the analysis.

The statistical processing stage was carried out using Epi Info™ and Microsoft Office 365 ProPlus tools.

Descriptive statistical indicators were calculated for the clinical and socio-demographic data of the patients.

Qualitative data were reported as frequencies (as numbers and percentages) and Fisher exact test was used for statistical processing.

Quantitative data were reported as medians with associated interquartile range, i.e. means with (±) standard deviation.

For the processing and interpretation of the results obtained, the Kruskall Wallis test was used.

Predictor variables were also determined using 10-variable logistic regression.

A value of $p<0.0001$ was considered statistically significant.

Although a p-value <0.0001 is less commonly used in high profile work, given the scale and importance of the research and the number of subjects used, by using a p-value <0.0001 the studies were overpowered to obtain very strong results regarding the clinical management of hypertension and the current profile of the patient with hypertension.

Given that the basis of the doctoral thesis is made up of 3 levels of study, the processing, interpretation and dissemination of the results obtained, respectively the highlighting of the conclusions have been broken down and highlighted separately.

For the study to outline the current profile of the patient with hypertension followed by outpatient services, the patients included have a mean age of 55.48 years, with a group median of 58 years.

Most are overweight or obese, have dyslipidemia described by high mean values of both total cholesterol and LDL component.

The median value of time from diagnosis of hypertension to admission is 7.56 years, with the best-represented group of patients suffering from 5-10 years of hypertension.

In this group, in terms of compliance to antihypertensive treatment, we can conclude that patients with high grades of hypertension (II and III) tend to be more compliant, but as time passes from diagnosis their aggregability to treatment decreases.

The degree of hypertension was directly correlated proportionally and strongly statistically significant with: age, BMI, total cholesterol and LDL component values, but also with time since diagnosis.

The latter correlation points to a worsening of the disease over time, but the exact reason is very difficult to prove statistically.

Age, BMI value, total cholesterol amount and degree of hypertension show a linear increasing trend with time since diagnosis, while elderly, dyslipidemic or smoking patients have more years since being diagnosed with hypertension and tend to be more compliant to treatment, while male, obese or higher degree of hypertension patients with high LDL-cholesterol values do not have a long period in years since receiving the diagnosis of hypertension and tend to be more non-compliant.

Surprisingly, mono/double/triple therapy for hypertension management is not a protective factor for a major neurological event, but they certainly prolong the life expectancy of the patient with hypertension.

Even though smoking patients have a higher aggregability to treatment, smoking is an individual risk factor for the occurrence of major neurological and cardiovascular events, but mono/double/triple hypertension management therapies are protective factors for the development of an acute myocardial infarction.

Following the creation and application of a correlation matrix reflecting the metabolic profile and age of patients with hypertension who referred to family doctors, the following results were obtained:
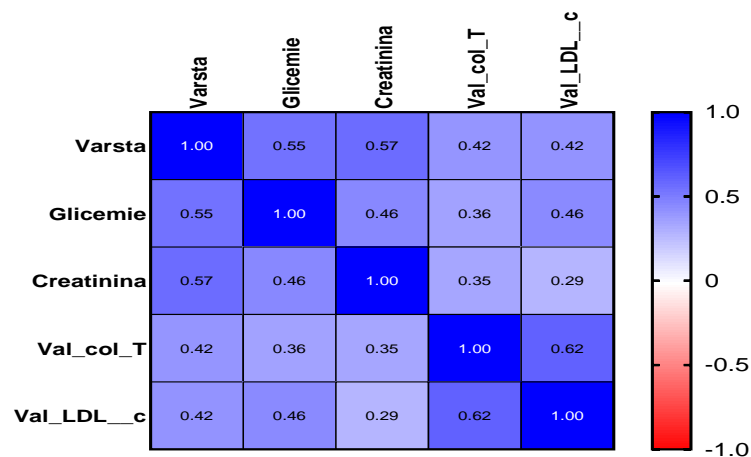
Source: own representation

Blood glucose values correlated directly proportional and strongly statistically significant with age (r=0.55), creatinine (r=0.46), total cholesterol (r=0.36), LDL (r=0.46). These correlation indices are supported by strongly statistically significant p-values (p<0.0001).

Creatinine values correlate with age (r=0.57), blood glucose (r=0.46), total cholesterol (r=0.35), LDL (r=0.29).

Regarding creatinine values, the following resulted:

Source: own representation

With regard to blood glucose values, the following results were obtained:

Source: own representation

To reveal the current profile, a logistic regression was performed using treatment compliance as the dependent variable and creatinine, blood glucose, total cholesterol, LDL and age as independent variables.

As for the study to outline the current profile of the hospitalized patient with hypertension, the patients included have a mean age of 60 years, with a group median of 61 years.

The majority are overweight or obese, have dyslipidaemia described by high mean values of both total cholesterol and LDL component.

The median time from diagnosis of hypertension to hospitalization is 8.03 years, with the best represented group of patients suffering from hypertension aged 5-10 years.

Regarding compliance to antihypertensive treatment, we can conclude that patients with high grades of hypertension (II and III) tend to be more compliant, but as time passes from diagnosis their aggregability to treatment decreases.

The degree of hypertension was directly correlated proportionally and strongly statistically significant with: age, BMI, total cholesterol and LDL component values, but also with time since diagnosis. The latter correlation points to a worsening of the disease over time, but the exact reason is very difficult to prove statistically. However, I do suggest that lack of aggregability to treatment is an important factor in the worsening of hypertension.

Age, BMI value, LDL amount and degree of hypertension show a linear increasing trend with time since diagnosis.

Even though smoking patients have a higher aggregability to treatment, smoking is an individual risk factor for major neurological and cardiovascular events.

Following the development and application of a correlation matrix mirroring the metabolic profile and age of patients with hypertension admitted to hospital, the following results were obtained:

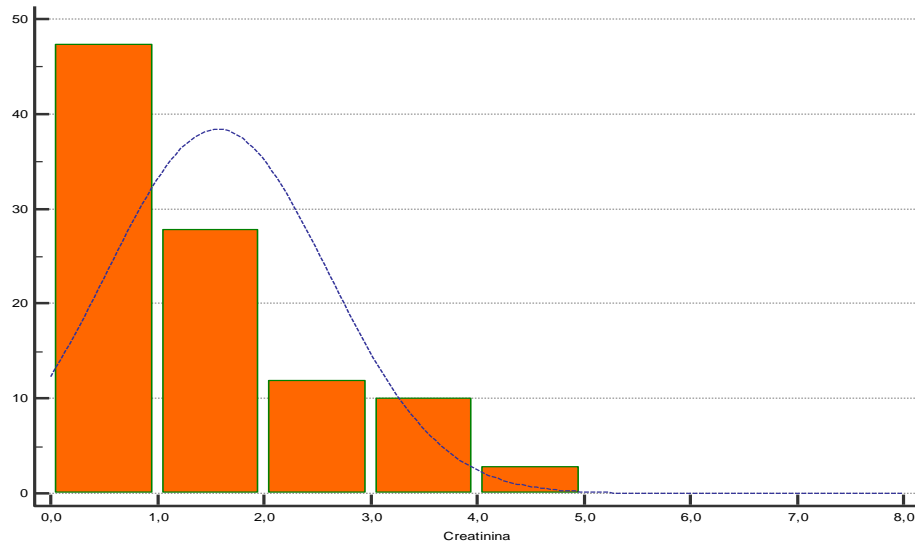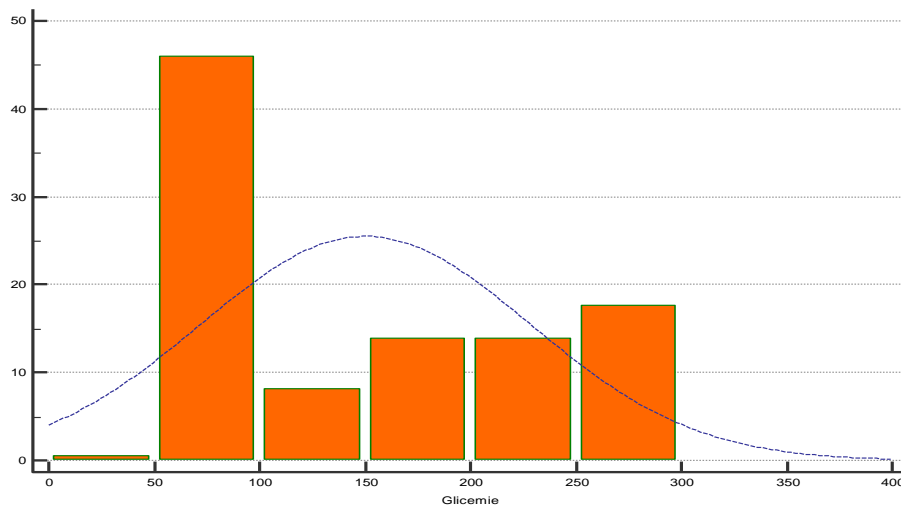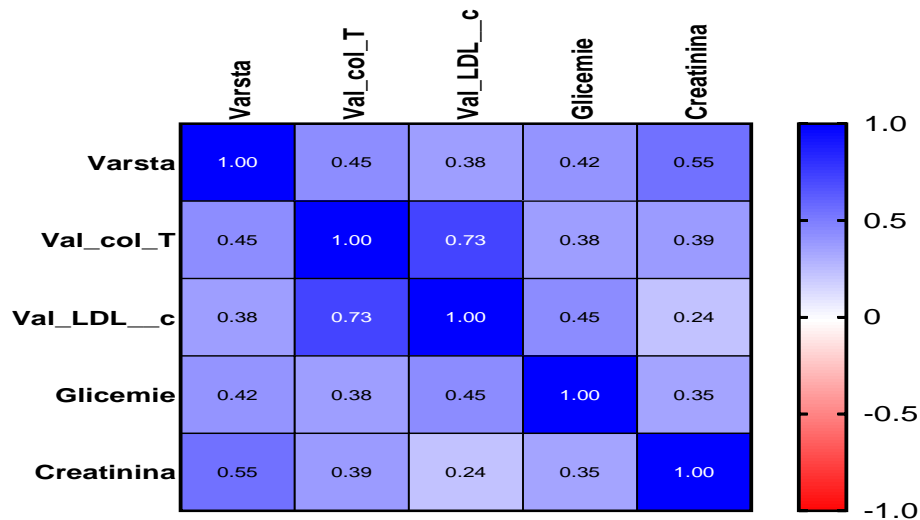Source: own representation

Blood glucose values correlated directly proportional and strongly statistically significant with age (r=0.42), creatinine (r=0.35), total cholesterol (r=0.38), LDL (r=0.45). These correlation indices are supported by strongly statistically significant p-values (p<0.0001).

Creatinine values correlate with age (r=0.55), blood glucose (r=0.35), total cholesterol (r=0.39), LDL (r=0.24).

Regarding creatinine values, the following resulted:
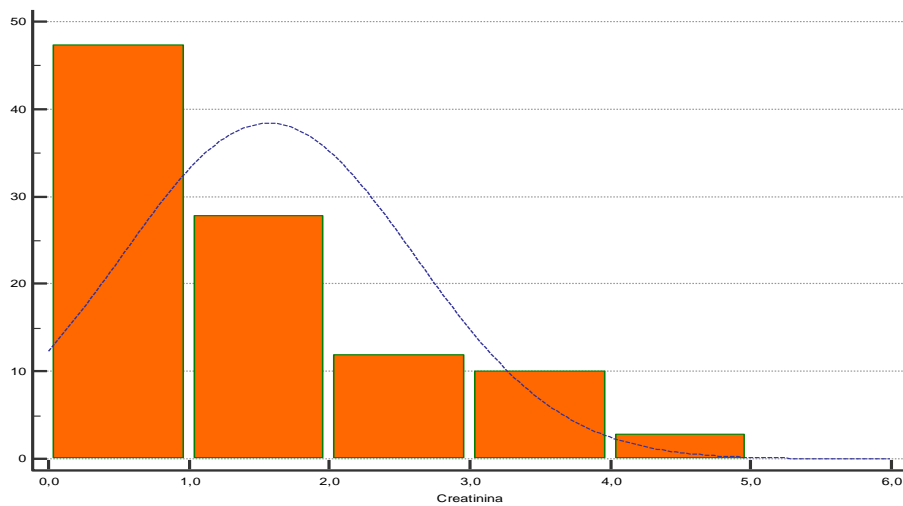
Source: own representation

With regard to blood glucose values, the following results were obtained:

Source: own representation

Even though the coefficients for total and LDL cholesterol have statistically significant values the OR values are very little different from 1 and cannot be called risk factors for lack of treatment aggregability.

Regarding the findings of the study on the impact of the COVID 19 pandemic on patients with hypertension, the approach highlighted that during the Sars-CoV-2 pandemic, patients' access to health care was restricted.
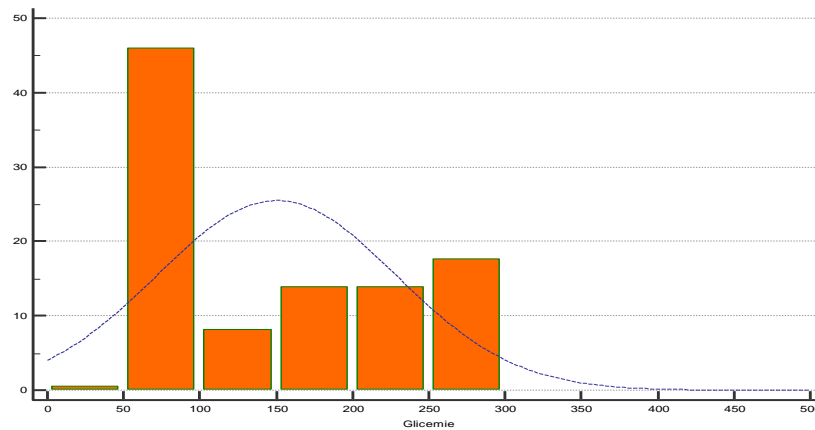
The long-term impact of this restriction is extremely difficult to quantify, but certainly the medium and long-term adverse effects will be extensive.

The psychological impact of the Sars-Cov2 pandemic (conscious) may aggravate certain pre-existing conditions - including hypertension.

Focusing human and financial resources predominantly on combating Sars-CoV-2 neglects the rest of the conditions. This attitude will indirectly increase morbidity and mortality from other causes.

The World Health Organization has noted that the highest mortality rate with COVID-19 is among elderly male patients, mainly those with pre-existing conditions.

Current statistics show that more than 40% of infected patients with severe forms of Sars-CoV-2 were hypertensive, and it is unclear whether hypertension alone, without other associated cardiovascular conditions, increases the risk of death from Sars-CoV-2.

It is also unclear whether successful management of hypertension results in a decreased risk of death from the new coronavirus.

The development of the PhD work revealed that we can discuss two simultaneous pandemics, namely a silent one generated by the evolution of hypertension and a conscious one, Sars - CoV-22.

In conclusion, hypertension is a real major public health problem and a significant cause of death worldwide, with an increasing incidence, and the costs associated with the prevention and treatment of this condition are a negative constant, with a macro impact on the economy.

Optimising the treatment of hypertension through the development of new therapeutic agents and innovative medical devices that can guarantee an optimal evolution of this pathology, with the least number of comorbidities and the least use of medical resources, will have a crucial beneficial effect on the rising costs of medical care and will create a climate for socio-economic development of both communities and nations.

As global public health undergoes a paradigm shift from „evidence-based medicine" to „value-based medicine", explicitly assessing and quantifying, in economic terms, the use of resources allocated to the clinical management of hypertension is the first step towards achieving the goal of providing the best possible evidence-based medical care in line with the current patient profile and cost-effectiveness.

Value-based medicine comes as a paradigm shift in the therapeutic management of hypertension, given the rise in both the cost and incidence of the condition, with the number of patients diagnosed estimated to triple by 2030.

The costs of managing hypertension include direct costs (related to prevention, diagnosis and treatment), indirect costs (including those related to complications of hypertension) and informal costs (work provided by unpaid personal carers, in most cases family members).

The current global socio-economic climate has led to a shift towards the concept of value called the „triple aim paradigm" (including distributive, technical and personal values).

This is why there is a need to integrate, even formally, cost analysis when developing hypertension guidelines, also taking into account factors such as opportunity cost, efficiency, benefits and cost-effectiveness.

At the same time, the scientific approach revealed that in the prescribing protocol for hypertension, reducing the number of antihypertensive drugs in the treatment regimen leads primarily to patient adherence to treatment, as well as reducing the incidence of cardiovascular events.

Although current treatment regimen guidelines state that a patient should be individually targeted for antihypertensive treatment, with reference to age, risk factors and comorbidities, risk of adverse drug reactions and impact of medication on quality of life, the premise of cost-effectiveness in the clinical management of hypertension should also be considered.

Starting from the premises highlighted by the Epidemiological Study on the Prevalence of Hypertension and Cardiovascular Risk in Romania - SEPHAR III, namely the 19.6% increase in the prevalence of the percentage of hypertension associated with deaths annually in our country, the realization of the research hypothesis and the objectives of the PhD thesis highlighted the following ideal characteristics of the cost-effective process in the clinical management of hypertension, namely:

a)   treatment should be based on evidence in the prevention of mortality and morbidity.

b)   in establishing the treatment regimen there should be evidence of benefit to the population groups for which it is intended to be used.

c)   the treatment must be tolerated.

d)   the regimen of treatment is one capsule per day, but which ensures control of hypertension for a minimum of 24 hours.

e)   the treatment is affordable and low cost.

The profile of the patient suffering from the condition of hypertension, which resulted from the study, is the patient who sums up the 3 conditions that define the metabolic syndrome, i.e. hypertension, a degree of obesity or overweight, respectively prediabetes or diabetes.

In order to increase adherence to treatment for such a patient profile, it is imperative that the combination treatment be as simple as possible and include all components and treatment strategies in one capsule, i.e. antihypertensives, statins and oral antidiabetics.

Given the current profile of the patient suffering from the condition of hypertension, fixed-dose antihypertensive combinations will lead to therapeutic compliance and tolerance for blood pressure reduction and long-term blood pressure monitoring, due to the optimal pharmacokinetic profile of the three representatives combined in a single pill.

Early diagnosis and early intervention through treatment and lifestyle changes significantly reduce the prevention and occurrence of complications that limit early retirement and reduce the patient's social and socio-economic disability.

Given that the pool of patients suffering from hypertension is between the ages of 18 and 60 years, it is necessary to screen for this condition at an early and middle age, and once

diagnosed, to start as early as possible with treatment and lifestyle changes required in all three conditions of the metabolic syndrome.

As hypertension is predominantly an asymptomatic disease, its detection should also be carried out through population screening programmes, as the implementation of structured population screening programmes will lead to the discovery of a large pool of patients who are currently unaware that they have hypertension.

Processing of the data obtained revealed that the current profile of the patient suffering from hypertension has changed in the last decade, the reason for neglect being "justified" by lack of symptomatology, lack of recognition of pathological importance, insufficient information, poor adherence to treatment, fear of adverse effects, but also by the following social determinants: globalisation, urbanisation, ageing, income, education and housing conditions.

This is why, in order to lower the overall cost of the condition, it is necessary to redefine patient information on how patients are aware of the severity of the condition in the medium and long term, the presentation of correct treatment information and the elimination or mitigation of adverse effects associated with drug treatment.

Hypertension control is far from satisfactory and remains the leading controllable cause of cardiovascular disease and global mortality in Europe. For this reason, and as a result of the new evidence gathered, the scientific research undertaken through the methodology applied has brought to light some original elements regarding the profile of the patient suffering from hypertension, which constitute a starting point for further scientific research, personal or of other specialists interested in this pathway represented by the need for cost efficiency in the clinical management of hypertension.

Reducing high blood pressure is an extremely important goal both for the health of an individual and for the economic health of a society, given that hypertension is a „silent disease” with no specific symptoms, and the implementation of the desideratum that „every child born in the new millennium has the right to live to the age of 65 without preventable cardiovascular disease” is a necessity for a better future.

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