THESIS

Study on the efficiency of the therapy with angiotensin converting enzyme inhibitors in hypertensive patients from Argeș County

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Study on the effectiveness of therapy with inhibitors of angiotensin converting enzyme in hypertensive patients in Arges County

Hypertension with its complications (HF, stroke, MI), is a real and important public health problem, especially for developed countries compared with the underdeveloped ones. HTA has acquired this status for several reasons:

⇒ it ranks as one of the first causes of cardiovascular mortality, reported by WHO (World Health Organization);
⇒ it is a disease itself as well as a risk factor;
⇒ it has a high prevalence and an uneven distribution;
⇒ it does not receive satisfactory control, which is objectified in achieving the target values recommended by the guidelines.

Hypertension treatment represents a key factor in preventing cardiovascular morbidity and mortality due to cardiovascular diseases. Thus, the optimization of antihypertensive treatment, rationally resulting in the reduction of cardiovascular morbidity and mortality, is a challenge for any clinician and scientific organizations that implement this approach in the development of guidelines useful in the detection, assessment and treatment of hypertension. In recent years, the treatment of hypertension has changed fundamentally and tends to be more appropriate and scientific. The discovery of antihypertensive drugs with actions at different levels of pathogenic chains, the possibility of drug selection in relation to individual factors and therapeutic trials achieved through rigorous methodology conducted on large groups of hypertensive patients, have allowed the development of certain treatment programs widely accepted.

Starting from the premise that the antihypertensive treatment recognizes multiple options, associations and it is not exclusively pharmacological, it allows the occurrence of various research perspectives of possibilities to improve the therapeutic regimen for patients with hypertension. Hypertension treatment is done in many countries at a suboptimal level, depending on the type of society, the degree of development of health systems and the availability of the economic resources.

This proves true for hypertensive patients in Arges County, too. Under the circumstances, the identification of an affordable and effective variant of antihypertensive therapy with minimal side effects and which can also be applied to multiple categories of hypertensive patients in Arges County (categories defined by age, associated pathology, their environment and lifestyle...
adopted by patients with hypertension) represents the major problem towards the approach of the research staff is oriented.

According to the results of multi-center clinical trial and to the recommendations of specialized organizations, materialized and included in management guidelines of hypertension and ACEI they represent an important class of antihypertensive drugs, highlighting both the therapeutic efficiency and the increased tolerability. They prove to be useful in initiating antihypertensive treatment, as monotherapy as well as in combining with a wide range of pharmacologically active substances, either as an associated therapy, or in fixed combinations.

Thus, the considerations of the treatment with ACE inhibitors as an effective antihypertensive therapeutic regimen that can be applied on hypertensive patients in Arges County are based on scientific arguments and justify the choice of this theme study. Under the circumstances, the major research problem acquires a distinct connotation, more accurately, that is the usefulness and effectiveness of ACE inhibitors in the treatment of patients with hypertension in Arges County.

The first phases are related to the need to analyze a 44-month-prevalence of hypertension among the patients hospitalized in Pitesti Emergency County Hospital and to the eloquence of the results, especially to their relevance for this doctoral study, by comparing them with the data available in the specialized literature. And in terms of actual results of the study, the analytical approach will also be a comparative one with the results of numerous investigations, in order to capture the main similarities and differences and to scientifically argue the conclusions specific to this theme.

The conducted retrospective analysis aimed at identifying the prevalence of hypertension in the population in Arges in order to parallel it with specific available data and from the targeted population segment it has been selected the group for the study referring to the efficiency of the ACEI therapy. It should be noted that the major group under study does not include all existing cases of hypertension in the county because the patients turn to primary health care network, specialized ambulatory, to municipal hospitals (Curtea de Arges, Câmpulung), to clinics and private practices, even to university clinics, given the relative proximity to Bucharest. Moreover, the real-time detection of hypertension among the large population and the awareness of the patients who suffer from this disease and act accordingly by submitting to a health professional check and follow an appropriate antihypertensive therapy, remain current and major issues for medical practice. This context does not allow identification of all hypertensive patients from Arges County, but it has made possible to outline a profile of a hypertensive patient in Arges County, insisting on the objectivity of those features that facilitate the optimization of antihypertensive therapy.
We believe that the size of the group under analysis (a total of 44,195 hospitalized patients with hypertension, out of which 11,827 in Cardiology), also coupled with the fact that we are talking about the largest hospital in the county, which includes the Department of Cardiology with medical staff and equipment at a standard of a county emergency hospital, where they particularly treat complex and complicated cases, compared to other units in the land, support the relevance of the obtained results and we can make a judgment regarding the prevalence of hypertension in Arges County. In fact, the national available indicators on the prevalence of hypertension in Romania were obtained under somewhat similar circumstances, since the studies targeted selected populations and did not provide representative data for the population of the whole country. The research carried out up to 2004 in south-western Romania revealed varied prevalence depending on the type of the selected population: 45.21% hypertensive of all the employees of an industrial unit, 69.1% hypertensive of a rural gipsy population or 76.34% of a population aged over 60, in rural areas. Study on a group of 365 over 35-year-old patients in Bucharest, shows a prevalence of 31.4%, out of which only 15% is controlled. Another study on a selected population was applied to the inhabitants of Urziceni, showing a prevalence of 32%.

The data obtained from this precursor study show a high rate of patients with hypertension in the cardiology ward (96.67%), together with a significant percentage (25%) in the whole hospital (with an average of about 42,000 patients), with 17.28% cases of hypertension newly discovered, without complications or onset hypertension, predominantly males (53.08%) from rural areas (62.20%), and the most affected age group is that over 60 (45.05%). The comparison of these indicators with the results of the SEPHAR must take into consideration the fact that the present study was not conducted by an active tracking among the population in the respective area, but by the retrospective analysis of a segment of hypertensive patients (those hospitalized in the Cardiology ward). The same problem should be taken into account for the study of the effectiveness of therapy with ACE inhibitors because it is prospective, observational, uncontrolled, for a period of 12 months, which covered a sample of hypertensive patients (with essential hypertension) who came to the Cardiology ward successively.

The process of evaluating of the effectiveness of ACEI therapy, adherence to this treatment and how this therapeutic schedule improves the hypertensive patient’s quality of life aimed at achieving the following objectives:

A. Demonstrating the effectiveness and efficiency of long-term therapy (6 months) with ACE inhibitors, aiming at decreasing the systolic and diastolic blood pressure;
B. Demonstrating the influence of ACE inhibitors on the level of total cardiovascular risk.

Moreover, the criteria by which the patients included in the study group and the findings of the
study were influenced, respectively ordered according to all these objectives, both for teaching reasons and for consistently revealing, for logically demonstrating, covering as many aspects, the efficiency of ACEI therapy in hypertensive patients from Arges county.

This doctoral project was divided into two major parts: the phase of knowledge and that of personal contributions. The first part contains data from specialty literature on hypertension, focusing on the global cardiovascular risk, on the renin-angiotensin-aldosterone system, by characterizing each component and highlighting their effects on target organs, the main ways to antagonize this system, the pharmacological aspects of ACE inhibitors and the results of the studies on the effects of ACE inhibitors on patients with cardiovascular damage. The part of personal contributions started with presenting the results of a retrospective study on hypertensive patients in Arges County a fact, whose importance and logic are being explained below. This doctoral study itself is the subject of a chapter of this paper, having the following subsections: objectives, materials and methods (the presentation of the studied group, the demographic profile of patients included in the lot, the situation regarding the cardiovascular risk of the group, criteria for inclusion / exclusion, ethical issues, operational plan of study, medical and statistical methods used, specifying the necessary equipment), results. Discussions on the final results and conclusions of this doctoral approach were included in separate chapters.

The study group included 357 patients with hypertension, from the case-book record in the Department of Cardiology, selected according to the inclusion and exclusion criteria already mentioned. The inclusion in the group started on the first of December, 2009 and ended on the thirty-first of May, 2010 so that to allow the proper ongoing of the clinical follow-up period - 6 months - for each patient. Whatever the time of study entry, each patient received the same operational plan. The full period of the study was 12 months. The study group represented 22.2% of all hypertensive patients (1608) hospitalized in the cardiology ward during the period of established enrollment. For the classification of subjects in different categories of blood pressure we used the ESH / ESC 2007 criteria and we took into account the details from the guideline in the management of hypertension regarding special cases such as isolated systolic hypertension (8.12% of the group). 11.2% of analyzed hypertensive patients were newly discovered (for newly-detected cases, the number of men is significantly higher than that of women \( p = 0.002391 < \alpha = 0.01 \) z test) whereas 88.79% of the patients with uncontrolled hypertension treatment, either because of suboptimal treatment, or because of low compliance, even null in various previous treatments (for known cases, the number of women is significantly higher than that of men \( p = 0 < \alpha = 0.01 \) z test). The percentage of newly-discovered hypertension lower than that of 22.9% resulted in the SEPHAR study at the level of the global group can be justified by reference to a larger population sample and not to the vast population in the noted study. The
same motivation supports, on the contrary, the relative similarity regarding the hypertension control (88.79% versus 93% - in the SEPHAR study, the control rate was 7%, so uncontrolled cases would be 93%), plus and precisely the aspect that unsatisfactory control of blood pressure showed the respective patients as eligible for enrollment.

**Hypertension represents a real public health problem for the county of Arges**, by the high prevalence in a population segment from Arges County. A percentage of 96.67% includes both the main diagnoses of hypertension and the secondary ones, with the predominance of the latter. Their statistical level, 5 times higher, is justified by the fact that frequent hospitalizations are caused by hypertension complications, not by the disease itself, and the existence of economic and financial reasons, due to the financing of the hospital, that is the DRG system, which influences the choice of coding in the sense of preferring it as a main diagnosis of hypertension complications. The comparison with the hypertension rates revealed by other national studies, such as SEPHAR, must be provided under the reserve that the present study was not conducted by an active tracking among the population in the area, but by the retrospective analysis of a segment of hypertensive patients.

**The demographic and cardiovascular profile of the hypertensive patient in Arges county** is similar to that of the patients with hypertension described in other studies. Its area of origin, the educational level, the age, the gender, the target organ damage and the risk factors are modulator markers of this profile. Within the target group, the prevalence of hypertension increases with aging, being higher in women over 60 years, along with menopause installation, while in the case of men, the predominance is at a younger age. The area of origin and the educational instruction level influence the hypertensive cardiovascular status in terms of access to medical services, to information, by valuing their own health status, by using information and ability to evaluate the quality of their own life on various levels (physical, cognitive, social, vocational, etc.). The analyzed hypertensive patients (357) accounted for a large number of major factors that are independent of the cardiovascular risks, as well as major cardiac, cerebral, renal, vascular damage, whose role in the pathology is clearly shown, but which can be controlled by therapeutic interventions, both pharmacological and non-pharmacological. The prevalence of LVH diagnosed both electrocardiographically (52.62%) and echocardiographically (66.11%) was quite high in the hypertensive group studied and was correlated with the severity of hypertension, its duration and the age of the patients. Ischemic heart disease was present in 48.18% of the patients in the study group with a higher prevalence of stable angina (28.85%). HTA proved to be a frequent cause of heart failure, which was identified in 63.30% of hypertensive patients under study. IMT ≥ 0.9 mm or atheroma plaque was diagnosed in 43.77% of the patients, out of which 26.41% were men and 17.36% were women. The ABI index is a
predictive test of the degree of stenoses in peripheral arteries of the legs. In the hypertensive group, 21.28% were diagnosed with moderate peripheral vascular disease, respectively 11.13% with severe peripheral vascular disease, totaling 32.41% of the patients with peripheral vascular disease. The prevalence of peripheral arterial disease (PAD) was more than two times higher among men than among women, respectively 24.09% as compared to 8.32%. Cerebrovascular damage was present in patients enrolled in the study in Arges County at a rate of 31.34%, with a double frequency among men (20.91%) as compared to women (10.43%). The most frequent cerebrovascular incidents were transient (18.56%). Microalbuminuria was detected in 39.26% cases of hypertensive patients under study. The metabolic syndrome rate ranked at a level of 60.5%, with the dominance of women (34.45%) as compared to the men (26.05%), in correlation with the obesity rate - 70.03% and a ratio B / F = 0.85 for this modifiable risk factor. 37.54% of our study group was associated to 1-2 risk factors, while 47.06% recorded an increase in the global cardiovascular risk by the association of more than three factors.

The ACEI represents an important class of antihypertensive drugs, highlighting both the therapeutic efficiency and accessibility, as well as the increased tolerability, useful in the initiation of various clinical situations associated with hypertension, as monotherapy and in combinations with a wide range of active pharmacological substances. The treatment with ACE inhibitors may be considered an effective antihypertensive therapeutic regimen that can be applied on hypertensive patients in Arges County.

The behavior under the ACEI therapy of the hypertensive patient from Arges county is not significantly different from that of hypertensive patients elsewhere or of other race, a conclusion supported by the comparative analysis of results obtained in this study with those revealed by randomized trials or meta-analyzes mentioned in the specialty literature.

Angiotensin converting enzyme inhibitors have been very effective, after 6 months of fair treatment, in lowering the blood pressure. It was found a significant decrease of SBP and DBP environments whereas the evolution was decreasing by the end of the study when the average pressure values had reached the recommended target guidelines (135/85 mmHg).

The ACE inhibitors reduce the hypertensive patient’s overall risk by multiple organ-protection objectified by the absence of hypertension complications during the course of the study and by the improvement of developmental stages, both the HTA and of the identified co-morbidities.

At many of the patients in the group, LVH, as well as the common complication of hypertension and predictive indicators of cardiovascular events, responded echocardiographically to the therapy with ACE inhibitors, by reducing the thickness of the
interventricular septum and of the posterior wall. Likewise, the ACEI study caused the transition of the analyzed patients from types of cardiac remodeling with poorer prognosis to types with improved prognosis.

To analyzed patients who were associated with HF (heart failure), the ACE inhibitors have improved effort tolerance, they have generated improvement in left ventricular ejection fraction and have delayed the progression to HF towards NYHA class III and IV. The increased exercise capacity could be appreciated in correlation with the quality of life, respectively the hypertensive patients have become more independent in providing daily activities, professional activities and self-care. Moreover, the family and socio-professional reintegration of this population of hypertensive patients in Arges County was precocious.

The hypertensive patients from Arges County treated with ACE inhibitors benefited from the restoration of the endothelial function, this fact being accomplished in a manner independent of the blood pressure, body mass index, waist, lipid fractions and basal glucose. Vascular remodeling was assessed by IMT and ankle-arm index. Under the therapy with ACE inhibitors, our group has not recorded cerebrovascular events. By controlling blood pressure and vascular remodeling, the ACE inhibitors improved glomerular filtration, with correction of microalbuminuria, slowing down the evolution towards chronic renal disease. The ACE inhibitors have controlled, ever since the initiation of the therapy, the blood pressure values, proving effective for 24 hours, without having adverse effects whose type and intensity could have required the removal of this pharmacological class from the therapeutic regimen and the interruption of the study. Proved tolerability, among other features, such as accessibility in terms of cost and availability of generic, manageability, have ensured good compliance of the hypertensive patients from the district of Arges to initiated therapy recommended on medium and long term.

The main goal of the ACEI therapy is to improve the quality of life of hypertensive patients, followed by the reduction of cardiovascular morbidity and mortality, a goal which has been achieved in the case of the respective studied group as well. Improving the quality of life for the hypertensive patients from Arges County treated with ACE inhibitors was evaluated by health self-assessment at the balance of study visit, by monitoring the hospitalization episodes and the periods of temporary disability during the treatment. The ACEI therapy on the studied group had a favorable socio-economic impact. The beneficial effects of the ACE inhibitors have been supported and enhanced by means of pharmacological measures (lifestyle changes), towards which the patients have shown a cooperative attitude.
DOCTORAL STUDY IMPACT – The impact of the presented doctoral approach can be expressed by:

The clinical impact – the detection of the patients with hypertension in early stages and the early initiation of the drug therapy with pharmacological class (ACEI) that has beneficial effects on global cardiovascular risk, a good compliance from the patient and thus with significant results in reducing cardiovascular mortality and morbidity.

The educational impact - can be appreciated from two directions: from the specialists’ point of view and from the health education perspective of the hypertensive patient.

The data from this research project may be part of the teaching required for the training and specialization of resident doctors, family doctors and not least for the students of the faculties and health care (nurses). It can also become useful in continuous medical education, being provided at various conferences / symposia / workshops and published in professional journals.

About patients, those enrolled in the study benefited from a multitude of information on hypertension and its complications, on the methods of investigation and treatment. They also stressed the importance of lifestyle changes and the type of behavior changes, causing the patient to realize the value of their health status and learn how to maintain optimal quality of life in the presence of hypertension.

The social impact – increasing the quality of life and the survival of the hypertensive persons, who return very early to their family and socio-professional environment due to the ACEI therapy.

The economic impact - reducing healthcare costs by optimizing the diagnostic and therapeutic act.