

THE EFFECTIVENESS OF THE THERAPY WITH ANGIOTENSIN CONVERTING ENZYME INHIBITORS IN THE HYPERTENSIVE PATIENTS FROM ARGEȘ COUNTY

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Keywords:

hypertension (High Blood Pressure), Angiotensin converting enzyme inhibitors (ACEI)

Abstract: Hypertension (High Blood Pressure) with its complications is a real and important public health problem even for the county of Argeș. Angiotensin converting enzyme inhibitors (ACEI) appear as a pharmacological class recommended to be used in most clinical situations in which hypertension is present. The aim of the present study is to demonstrate the efficacy of the ACEI therapy in a group of hypertensive patients from Argeș County and the influence of this treatment on global cardiovascular risk. The study results concluded that the ACEIs are effective in lowering systolic and diastolic blood pressure, they reduce global cardiovascular risk through multiple organ-protection and prevention of complications and they are an appropriate antihypertensive treatment for the hypertensive patients from Argeș County, with a favourable socio-economic impact.

Cuvinte cheie:

hipertensiunea arterială (HTA), inhibitori ai enzimei de conversie a angiotensinei (IECA)

Rezumat: Hipertensiunea arterială (HTA), alături de complicațiile sale, constituie o reală și importantă problemă de sănătate publică pentru județul Argeș. Inhibitorii enzimei de conversie a angiotensinei (IECA) apar drept o clasă farmacologică recomandată a fi utilizată în mai toate situațiile clinice în care este prezentă HTA. Scopul studiului prezent este de a demonstra eficacitatea terapiei cu IECA la un lot de 357 hipertensivi argeșeni și influența acestui tratament asupra riscului cardiovascular global. Rezultatele studiului au condus la concluzia că IECA sunt eficienți în scăderea valorilor tensionale sistolice și diastolice, reduc riscul cardiovascular global prin organoprotecție multiplă și prevenirea apariției complicațiilor și sunt o schemă de tratament antihipertensiv potrivit pacienților argeșeni cu HTA, având un impact socio-economic favorabil.

INTRODUCTION

Hypertension (High Blood Pressure) with its complications is a real and important public health problem, especially for the developed countries, as compared to the underdeveloped ones. Hypertension has acquired this status for several reasons: it ranks first among the causes of cardiovascular mortality, reported to WHO (World Health Organization); (1) it is a disease itself, as well as a risk factor; it has a high prevalence and an uneven distribution; (2) it does not benefit from a satisfactory control, a control materialized in achieving the target values recommended by the guidelines.

Hypertension treatment is a key factor in preventing cardiovascular morbidity and mortality. Thus, the optimization of the antihypertensive treatment, resulting in the rational reduction of cardiovascular morbidity and mortality, is a challenge of any clinician and scientific organization that implement this approach in the development of guidelines useful in the detection, assessment and treatment of hypertension. The discovery of antihypertensive drugs with actions at different levels of the pathogenic chains, the possibility of drug selection in relation to the individual factors and therapeutic trials, made with rigorous methodology on large groups of hypertension patients, have allowed the development of treatment programmes widely accepted.

RESEARCH HYPOTHESIS

Starting from the premise that antihypertensive treatment recognizes multiple options, associations and it is not exclusively pharmacological, different perspectives are opened

regarding the research possibilities to improve the therapeutic treatment for the patients with hypertension. This proves to be true for the hypertensive patients in Argeș County, too. Under these circumstances, the identification of an accessible and effective way of antihypertensive therapy (treatment with ACEI) with minimal side effects and which can be applied to multiple categories of hypertensive patients from Argeș county (categories defined according to age, associated pathology, environment and lifestyle adopted by the patients with hypertension) is a major problem towards which our research approach is oriented. Furthermore, the purpose is to demonstrate the efficacy of the therapy with angiotensin converting enzyme inhibitors (ACEI) in the hypertensive patients from Argeș County

OBJECTIVES

The process of evaluating the effectiveness of ACEI therapy, the adherence to this treatment and how this therapeutic scheme improves the lifestyle of the hypertensive patients aimed at achieving the following objectives:

1. Demonstrating the effectiveness and efficiency of ACEI therapy on medium term (6 months) in decreasing the systolic and diastolic blood pressure;
2. Demonstrating the influence of ACEI on the level of total cardiovascular risk.

METHODS

The study group included 357 patients with hypertension from the casuistry of the Department of Cardiology (22.2%) selected according to the specified inclusion

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CLINICAL ASPECTS

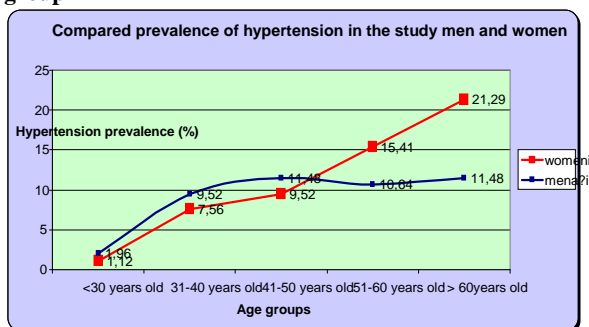
and exclusion criteria. The inclusion in the batch started on the 1st of December 2009 and ended on the 31st of May 2010, so as to allow the proper conduct of the follow-up period of 6 months for each patient. Whatever the time of the study entry, each patient received the same operational plan. The full study period was 12 months. The study group represented 22.2% of the total hypertensive patients (1608) admitted into the Department of Cardiology during the established enrolment. For the classification of subjects in different categories of blood pressure, we used ESH/ESC criteria from 2007 and we took into account the details of the respective management guide of hypertension in special cases, such as isolated systolic hypertension (8.12% of the group). 11.2% of the hypertensive patients analyzed were newly discovered (for newly-detected cases, the number of men is significantly higher than the number of women $p = 0.002391 < \alpha = 0.01$ z test), while 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 the number of men $p = 0 < \alpha = 0.01$ z test).

Methods used in this study: medical methods (history, physical examination, para-clinical explorations – electrocardiogram, Doppler ultrasound and echocardiography, laboratory tests); statistical methods.

RESULTS

The demographic and cardiovascular profile of the hypertensive patients from Argeş County is similar to that of the patients with hypertension described in other studies. The area of origin, the educational level, the age, the gender, the target organ damage and the presence of the risk factors are modulator indicators of this profile. Within the target group, the prevalence of hypertension increases with age, being higher in women over 60, along with menopause, while the male predominance is at younger age.

Figure no. 1. The prevalence of hypertension in the study group



The area of origin and the educational level influence the hypertensive patients' cardiovascular status in terms of access to medical service, information, by valuing their health status, the use of information and ability to judge the quality of life on various level (physical, cognitive, social, vocational, etc.). Analyzed hypertensive patients (357) accounted for a large number of major factors and independent of cardiovascular risk, as well as major cardiac, cerebral, renal, and vascular damage, whose role in pathology is clearly shown, but which can be controlled by therapeutic interventions, both pharmacological and non-pharmacological. The prevalence of LVH (Left Ventricular Hypertrophy) evaluated both electrocardiographically (52.62%) and echo-cardiographically (66.11%) was quite high in the studied hypertensive group and correlated with the severity of hypertension, its duration and the

age of the patient. The ischemic heart disease was present in 48.18% of the patients in the studied group with a higher prevalence of stable angina (28.85%). Hypertension proved to be a frequent cause of heart failure, which was identified in 63.30% of the studied hypertensive patients. IMT ≥ 0.09 mm (intimate medium thickness) or atheroma plaque were diagnosed in 43.77% of patients, of which 26.41% were men and 17.36% were women. The AAI index (ankle-arm 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. The prevalence of peripheral arterial disease (PAD) was over two times higher among men than women, respectively 24.09% to 8.32%. Cerebral-vascular damage was present in the patients included in the study in the Argeş County at a rate of 31.34% with a double frequency in men (20.91%) than women (10.43%). The most frequent cerebral-vascular events were the ischemic transient accidents (18.56%). Micro-albuminuria was detected in 39.26% of the analyzed hypertensive patients. The rate of the metabolic syndrome stood at a level of 60.5% with the dominance of women (34.45%) as compared to men (26.05%) in correlation with obesity rate (70.03%) and the M/W ratio = 0.85 for this modifiable risk factor. 37.53% of the patients of our study were associated with 1-2 risk factors, while 47.06% recorded an increase in global cardiovascular risk by associating more than three factors.

DISCUSSIONS

The effectiveness and efficiency of the ACEI therapy on medium term (6 months) in decreasing the systolic and diastolic blood pressure

At the reference visit (RV – corresponding to the admission time), they had an average of the SBP (systolic blood pressure) of 175 mmHg and the DBP (diastolic blood pressure) was at an average level of 100mmHg. In these patients, the ACEI therapy was initiated according to their blood pressure, to co-morbidities and to the damage of target organs. Given the above-mentioned, I opted for one of the three options: monotherapy, the association of the ACEI with other antihypertensive agents and drug combinations. At V1 visit, we monitored not only the SBP and DBP but also the patients' tolerability to ACEI, tolerability expressed by the presence or absence of the adverse reactions, analyzed as type and intensity. It should be noted that all patients tolerated the treatment well, no side effects were identified that could require the disruption of the trial and consequently, the treatment schema went on.

For SBP, the values between visits in the patients in the study group decreased significantly $p = 0.002335 < \alpha = 0.01$; between RV and V4 $p = 0 < \alpha = 0.01$, SBP regression having a statistic significance.

For DBP, between RV and V1, there was not a significant decrease ($p = 0.136328 > \alpha = 0.01$); favourable evolution, in the sense of down warding the diastolic blood pressure values, started to reveal itself from V2; thus, between V1 and V2, there is a significant decrease ($p = 0.047034 < \alpha = 0.05$), the same situation between V3 and V4 ($p = 0.0000097 < \alpha = 0.01$); between RV and V4, $p = 0 < \alpha = 0.01$, so it is statistically significant.

The recordings of SBP and DBP at 4 weeks (V2) showed average values of 165 to 95 mmHg, the downward tendency of the values not being relevant; therefore in the patients uncontrolled therapeutically with one of the schemes originally chosen, changes were made in the treatment strategy: monotherapy was replaced with associated therapy or combinations, the replacement of the ACEI type, the option for

CLINICAL ASPECTS

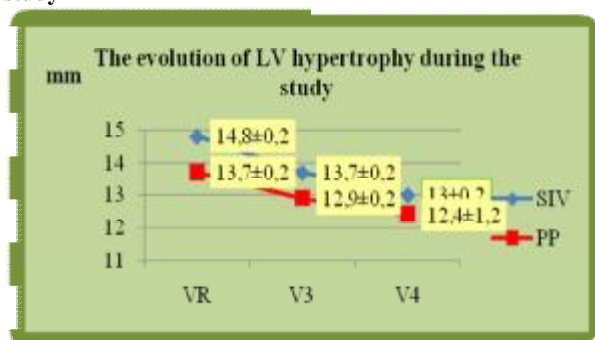
bi or triple therapy including an ACEI or the replacement of the therapeutic combination which also included an ACEI. The goal of these therapeutic changes was to achieve the target blood pressure values, as well as to obtain target organ protection. Note that at this visit, there were not reported side effects and all patients could continue the study.

The effectiveness and efficiency of the ACEI therapy were visible after 3 months of treatment, respectively at visit V3, when it was found a significant decrease of medium SBP and DBP, while the evolution was decreasing by the end of the study (V4 – 6 months) when the values of the blood pressure reached the target levels recommended by the guidelines (135/85 mmHg).

The effects of ACEI on LVH by preventing remodelling

The administration of antihypertensive treatment in patients with essential hypertension stage II and III has demonstrated the effectiveness of ACEI in reducing the thickness of inter-ventricular septum and of the posterior wall (for both variables $p < 0.001$).

Figure no. 2. The evolution of LV hypertrophy during the study



At the study group, the type distribution of LVH was as follows: concentric remodelling (with normal LVM or with high LVM) to 57.89% of the study group, the asymmetric LVH to 22.32% of the patients, respectively eccentric LVH to 19.79% of the rest of the patients. Under medication with ACEI for 6 months, visible improvement of the types of hypertrophy was observed, passing from the category with the worst prognosis to the category with more favourable prognosis (concentric remodelling and left ventricle with normal appearance).

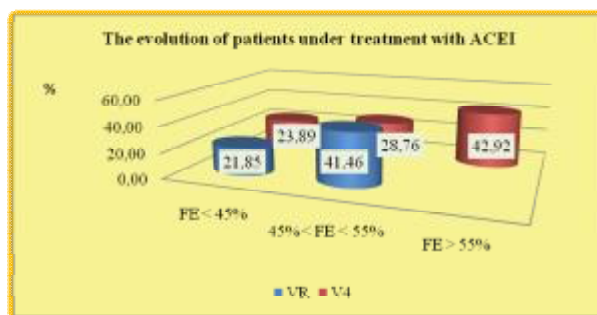
The evaluation of the therapeutic response in the patients with heart failure associated with hypertension

The evolution of these patients under treatment with ACEI is shown in the following table and chart:

Table no. 1. The evolution of patients under treatment with ACEI (by EF)

	VR (Reference visit)	V4 (balance visit)	p - t test
FE < 45%	78	54	0,273132 > $\alpha = 0,01$ no significant difference
45% < FE < 55%	148	65	0,00000000000000013 < $\alpha = 0,01$ significant difference
FE > 55%		97	

Figure no. 3. The evolution of patients under treatment with ACEI

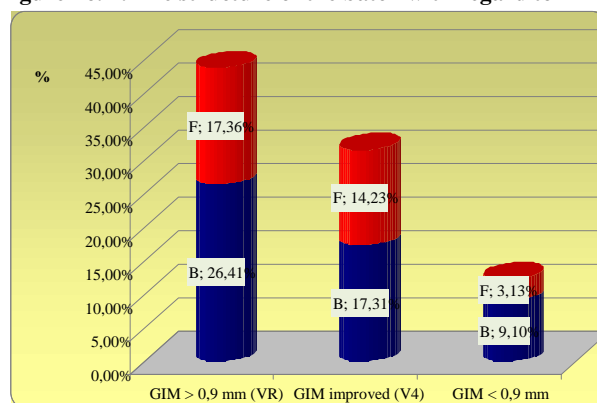


Assessing the influence of ACEI on vascular hypertensive and diabetic damage in the patients with hypertension

Table no. 2. The structure of the batch with regard to IMT (intimate medium thickness)

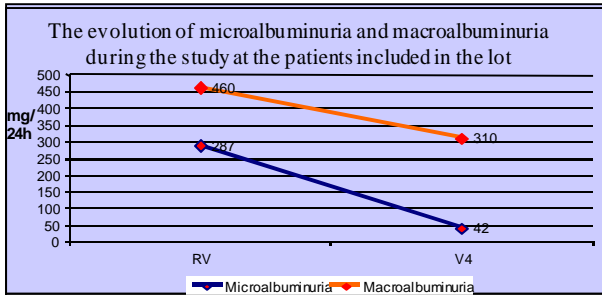
%	GIM > 0,9 mm (VR)	GIM ameliorated (V4)	GIM < 0,9 mm	p between VR și V4	p between V4 and GIM < 0,9 mm
B	26,41%	17,31%	9,10%	0,00229693 9 < $\alpha = 0,01$ significant difference	0,002260271 < $\alpha = 0,01$ significant difference
F	17,36%	14,23%	3,13%	0,00206094 1 < $\alpha = 0,01$ significant difference	0,002381312 < $\alpha = 0,01$ significant difference
Total	43,77%	31,54%	12,23%	0,00243021 3 < $\alpha = 0,01$ significant difference	0,002757837 < $\alpha = 0,01$ significant difference
p between B and F	0,0022948 65 < $\alpha = 0,01$ significant difference	0,00205906 1 < $\alpha = 0,01$ significant difference	0,00217 < $\alpha = 0,01$ significant difference		

Figure no. 4. The structure of the batch with regard to IMT



The demonstration of the effect of ACEI on microalbuminuria – the medium level of the microalbuminuria of the study group showed a significant decrease in V4 in comparison to VR by 85.37% ($p=0<0.01$; t test); in the same conditions, the decrease of macroalbuminuria by 32.61% was achieved ($p=0<0.01$; t test).

Figure no. 5. The evolution of microalbuminuria and macroalbuminuria during the study in the patients included in the batch

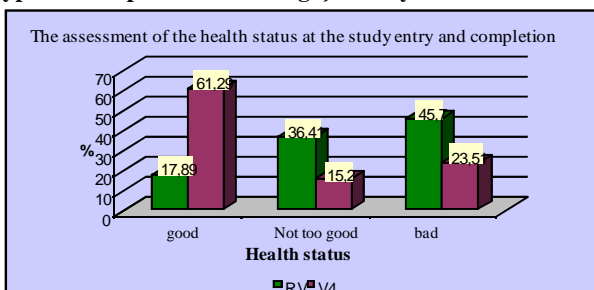


The evaluation of tolerability and safety on medium-term for ACEI – dry cough, explained by increasing bradykinin and prostaglandin has been reported in a number of 8 of 357 patients ($p=0<0.01$ shows that the number of patients without any side effects is significantly higher), but it was not annoying and persistent to lead to giving up ACEI in the treatment scheme, but only a possible replacement of the preparation. (e.g., replacing enalapril with perindopril). Note that all patients completed the study, not being necessary to abandon the study because of the side effects.

Improving the quality of life for the patients with hypertension, assessed by processing the data obtained from a questionnaire applied on the quality of life at the entry and completion of the study.

The analysis of collected data revealed the following situation regarding the studied patients ‘assessment of their own health status:

Figure no. 6. The assessment of the health status of the hypertensive patients from Argeş County



According to the evidence in the chart above, the health status of the hypertensive patients treated with ACEI, perceived individually, has improved significantly (the transition from lower-status categories of bad or not very good health status, to higher categories with $p = 0.000003032<0.01$, respectively $p = 0.000001106<0.01$ – statistically significant t test).

CONCLUSIONS

1. Hypertension is a real public health problem for Argeş County through high prevalence in a population segment from Argeş County (the Department of Cardiology, Piteşti County Emergency Hospital – 96.67 % with a significant percentage – 25% which records a yearly average of 42.000 patients at the level of the entire hospital). The percentage of 96.67% includes both the main diagnoses of hypertension as well as 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 the complications of hypertension, not by the disease itself, and by the existence of economic and financial reasons, due to the financing of the hospital, the

DRG system that is, which influences the choice of coding, in the sense of preferring as main diagnosis the hypertension complications. Comparisons to the frequency of hypertension revealed by other national studies, such as SEPHAR (3) must be restricted by the fact that the present study was not conducted by an active screening of the population in the area, but through a retrospective analysis of a segment of hypertensive patients.

- The demographic and cardiovascular profile of the hypertensive patients in Argeş County is similar to that of the patients with hypertension described in other studies.
- ACEIs are an important class of hypertensive drugs, highlighting both the therapeutic efficiency and accessibility and by increased tolerability, useful in initiating the treatment of various clinical situations associated with hypertension, such as monotherapy, as well as in combinations with a wide range of active pharmacological substances. The treatment with ACEI may be considered an effective antihypertensive scheme that can be also applied to the hypertensive patients in Argeş County.
- The behaviour under the ACEI therapy of the hypertensive patients in Argeş County is not significantly different from that of the hypertensive patients elsewhere or of another race, a conclusion supported by a comparative analysis of the results obtained in the current study with those revealed by randomized trials or by meta-analyses mentioned in the literature.
- The angiotensin converting enzyme inhibitors have been very effective in lowering blood pressure after a fair treatment of 6 months. It was found a significant reduction of medium SBP and DBP, whereas the evolution was decreasing by the end of the study when the medium blood pressure values reached the target level recommended by the guidelines (135/85 mmHg).
- The ACEI 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 of both hypertension and of identified comorbidities.
- In many patients in the group, LVH, the common complication of hypertension and the predictive markers of cardiovascular events, the response to therapy with ACEI showed echo-cardiographic response by reducing the thickness of the inter-ventricular septum and the posterior wall. The ACEI study also led to the crossing of the studied patients from cardiac remodelling types with poorer prognosis to types with improved prognosis.
- For the analyzed patients who also suffered from HF (heart failure), the ACEI have improved exercise tolerance, have generated improvement in the ejection fraction of the left ventricle and delayed the progression of HF towards III and IV NYHA class. Increased exercise capacity could be appreciated in correlation to the quality of life, respectively the hypertensive patients have become more independent in providing professional and self-care daily activities. Moreover, family and social-professional reintegration of this population of hypertensive patients in the Argeş County was even earlier.
- The hypertensive patients from Argeş County treated with ACEI benefited from the restoration of endothelial function, this being accomplished in a manner independent of the blood pressure, body mass index, waist, lipid fractions and fasting glucose. Vascular remodelling was assessed by IMT and ankle-arm index. Under therapy with ACEI, our group has not recorded cerebral-vascular events.

CLINICAL ASPECTS

10. By controlling blood pressure and vascular remodelling, the ACEI improved glomerular filtration, by correcting micro-albuminuria and by slowing the progression of chronic renal disease.
11. Ever since the initiation of the therapy, the ACEI have controlled the blood pressure values, proving effective 24 hours, without the kind and intensity of adverse effects requiring the removal of this class of pharmacological regimen and the discontinuation of the trial. Proved tolerability, among other features, such as accessibility in terms of cost, generic availability and manageability have insured a good compliance of the hypertensive patients from Argeş County to the therapy initiated and recommended on medium and long term.
12. The main goal of ACEI therapy is to improve the quality of life of hypertensive patients, followed by the reduction of morbidity and mortality, a goal that has been achieved for the study group.
13. Improving the quality of life of the hypertensive patients in Argeş County treated with ACEI was evaluated by the self-assessment of the health status at the final visit, by monitoring the periods of hospitalization and the periods of temporary work disability during the treatment. The ACEI therapy on the study group had a favourable socio-economic impact.
14. The beneficial effects of ACEI have been supported and enhanced by means of pharmacological measures (lifestyle changes), to which patients have shown a cooperative attitude.

REFERENCES

1. Ghidul pentru managementul HTA, Revista Română de Cardiologie. 2007;22(3).
2. Muşetescu R. Cardiologie, Editura Medicală Universitară, Craiova; 2008.
3. Dorobanţu M, Darabont R, et al. Studiul SEPHAR-studiu de prevalenţă a hipertensiunii arteriale şi evaluare a riscului cardiovascular în România, Revista Română de Cardiologie. 2006;21:2.