

Review

**By Prof. Ivan Tomov Gruev, MD, PhD
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for the PhD thesis of master pharmacist Stefka Stoyanova Stoyanova

on the topic:

**ANALYSIS OF DIAGNOSTIC AND THERAPEUTIC STRATEGIES
IN PATIENTS WITH ARTERIAL HYPERTENSION BY THE METHODS OF
MEASURING DRUG UTILIZATION
AND RATIONAL DRUG USE AT THE MACRO LEVEL
IN BULGARIA**

**Regarding the procedure for obtaining the scientific-educational degree "Doctor of
Pharmacy"**

Field of higher education – 7. Health care and sports

Professional field – 7.3 Pharmacy

Scientific specialty "Social Medicine and Organization of Healthcare and Pharmacy"

Supervisor

Prof. Emil Hristov, MD, PhD

I declare that I have no conflicts of interest in relation to this PhD thesis and find no evidence of plagiarism.

Master pharmacist Stefka Stoyanova was enrolled as a regular PhD student by order № 20-937 of the Rector of Sofia University "St. Kliment Ohridski", from 09.07.2020 and on 10.07.2023 was successfully dismissed by order 20-1284 of 25.07.2023.

The PhD thesis was discussed and directed for defense by the Department of Physicochemistry, Faculty of Chemistry and Pharmacy, Sofia University "St. Kliment Ohridski", Sofia, Bulgaria.

The defense materials are available at the Department of Physicochemistry, Faculty of Chemistry and Pharmacy, Sofia University "St. Kliment Ohridski", Sofia, Bulgaria.

Master pharmacist Stefka Stoyanova graduated from Mathematics High School "Atanas Radev" – Yambol and graduated Pharmacy at Sofia University "Kliment Ohridski", Sofia.

Since 16.10.2023 she has been pointed to the position assistant professor at the Faculty of Chemistry and Pharmacy of Sofia University "Kliment Ohridski".

Significance of the problem:

Arterial hypertension is a major risk factor for cardiovascular morbidity and mortality, with a particularly high burden for the development of stroke.

In Bulgaria, the prevalence of hypertension is about 55%, compared to the European prevalence of 30-45%. There are about 2 million hypertensives in Bulgaria, but in recent years only about 37% of them are adequately treated, with control achieved. Overweight, obesity and a sedentary lifestyle are considered to be major risk factors, also not forgetting smoking and alcohol consumption.

The PhD thesis is well structured and illustrated. It consists of : 124 pages and is illustrated with 19 tables and 45 figures. The literature used includes 189 sources. The literature review is extensive and comprehensive.

The aims of the PhD thesis are clearly stated:

The primary aim of the study is to analyze the drug utilization in the treatment of uncomplicated essential hypertension in Bulgaria using quantitative and qualitative measures at national level.

Secondary aim – to evaluate the obtained data through the prism of rational use of medicines by determining the compliance of diagnostic and therapeutic strategies in patients with uncomplicated essential hypertension with treatment standards and valid national and international pharmacotherapeutic guidelines.

Nine tasks are set:

1. Analysis of national programs for prevention of arterial hypertension.
2. Determination of the total number of patients diagnosed with primary hypertension who are part of the reimbursement system. Percentage of patients with different types of complication of primary essential hypertension (classified according to the International Classification of Diseases (ICD)).
3. Indication of the most prescribed medicines by INN according to the costs paid by the NHIF budget.
4. Identification of the most prescribed medicinal products by INN, defined as absolute number of DDD.
5. Presentation of the cost of medicinal products calculated as number of packages.
6. Identification of the top ten mono-medicinal products by INN, quantity of active substance and number of tablets per package, calculated according to the DDD/per patient/per year.
7. Definition of the most prescribed combination medicinal products as cost containing fixed dosage forms by trade name and INN.
8. Specify the most prescribed combination medicinal products as DDD/year containing fixed dosage forms by trade name and INN.
9. Calculation of DDD per capita of the population for 1 year and DDD per 1000 capita of the population for 1 year.

Materials and methods:

Study design – retrospective, observational study of data bases.

Study period January 2017 – December 2021.

Publicly available data from the registers of the National Health Insurance Fund (NHIF) related to arterial hypertension, classified according to the International Classification of Diseases (ICD) code I10 - Essential (primary) hypertension – number of patients, reimbursement amount, types of medicinal products by INN (international non-proprietary name), products by trade names were analyzed.

Drug utilization analyses were performed according to the WHO's ATC/DDD methodology.

The registration status of the medicinal products has been checked and is consistent with the data from the public registers of the EMA and the BDA.

Results were processed using descriptive statistical methods and presented in absolute and relative values, mean, median, mode.

Results:

A fundamental basis for measuring rational use and drug utilization is the availability of accurate epidemiological data that can be derived from properly maintained disease registries at the national level.

Unfortunately, such registries are not maintained in Bulgaria and we refer to extrapolations from literature data and from data of other countries that are comparable in demographic and socio-economic development to Bulgaria.

According to epidemiological and literature data, there should be between 1 750 000 – 2 000 000 people with essential arterial hypertension, either uncomplicated or complicated, in Bulgaria.

According to the NHIF, patients with different types of hypertension whose treatment is reimbursed are between 1 393 037 and 1 099 608 people.

There is a statistically significant deviation between epidemiological and reimbursement data, ranging from 350 000 to 500 000 people.

A possible reason for this is that a large proportion of patients pay for their own and are not included in the NHIF statistics, or this difference is due to cases of undiagnosed hypertension. These suspicions should be the subject of further research.

The cost of treating patients with essential hypertension (ICD I10) for the five-year period 2017-2021 amounted to BGN 41 137 809. The total budget for treatment with medicinal products of outpatients is BGN 6 478 389 587.

In a summary analysis based on DDD, INN and cost per number of packages, what impresses is that in Bulgarian therapeutic practice the most prescribed products are beta-blockers, calcium antagonists and centrally acting anti-adrenergic agents. ARBs are predominantly represented by Valsartan. In all cross-sectional analyses, the significant use of Lercanidipine is striking.

Medicinal products containing a single active substance are preferred in uncomplicated essential hypertension. They occupy 2/3 of the prescription compared to combination medicinal products, although new trends are to start treatment of essential hypertension directly with fixed-dose combinations.

Conclusions based on the results – 12.

Well described in the PhD thesis.

Contributions (as formulated in the PhD thesis):

Contributions of scientific and theoretical nature and originality of the PhD thesis

- 1.** For the first time in Bulgaria an analysis of diagnostic and therapeutic strategies in patients with arterial hypertension is performed by measuring drug utilization and rational use of medicines.
- 2.** For the first time, a systematic review of scientific publications on the PRISMA standard for assessing diagnostic and therapeutic strategies in patients with arterial hypertension is performed.
- 3.** For the first time in Bulgaria, a retrospective comparative analysis between epidemiological and reimbursement data is conducted to assess the prevention and treatment effectiveness of socially important diseases.
- 4.** The study reveals new theoretical and applied aspects of retrospective analyses of health insurance data records and, in particular, how to use reimbursement data to ration therapies for socially important diseases.

Methodological contributions

- 1.** An original approach was developed to assess the positive and inverse relationships between effective prevention, timely diagnosis, evidence-based treatment, reimbursement, cost-effective therapies, and health outcomes by measuring drug utilization (quantitative parameters).

Confirmative contributions

- 1.** The introduction of rational use criteria in clinical practice and reimbursement systems should become a mandatory element of medicines policy.

Publications associated with the PhD thesis: presented with 7 publications, 2 in refereed and 5 in non-refereed journals, in all master pharmacist Stoyanova is first or second author.

Conclusion: The PhD thesis of master pharmacist Stefka Stoyanova Stoyanova represents a thorough study of the therapeutic practices for the treatment of AH in the Republic of Bulgaria. In the course of the presentation, the PhD student shows a thorough knowledge of the scientific literature, as well as good abilities to collect, analyze and summarize the obtained results. I particularly appreciate the critical analysis of the NHIF data. The recommendations made do not diminish the value of the proposed PhD thesis, which fully meets the criteria of the Law for the development of academic staff of the Republic of Bulgaria and the regulations of the Sofia University "St. Kliment Ohridski" for the award of the scientific-educational degree "Doctor". Therefore, I recommend the esteemed members of the scientific jury to vote positively for the award of the scientific-educational degree "Doctor" to master pharmacist Stefka Stoyanova.

13.11.2023 г.

Reviewer

Sofia

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