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Clinical-epidemiological and pharmacoepidemiological investigation of acute cerebrovascular accidents

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ABSTRACT

Acute cerebrovascular accidents belong to leading causes of disability and death worldwide, in Ukraine in particular. Hence, proper medical-and-pharmaceutical aid is crucial for the positive outcomes. Our clinical-epidemiological analysis of inpatient medical records showed that ACVA occurred in 77.6% of male and 76.0% of female patients aged 50 and over. Cerebral infarction was diagnosed in 50.3% of patients, 44.3% – sequelae of cerebrovascular disease, and 8.7% – cerebral hemorrhage. Hypertension was the prevalent concomitant disorder, with the rate of 82.0% of cases. The content-, frequency-, ABC, ATC/DDD, DU 90% analyses, and generalization allowed establish the trends, amounts and structure of drug consumption. Among 198 of drugs, the max specific weight belonged to those effecting on cardiovascular system (29.8%). We identified 8 most frequently prescribed drugs. High rates of consumption were typical for 3 drugs. The 90% of consumed DDDs accounted for 45 drugs. Atorvastatin, Dexamethasone, and Enoxaparin were characterized by high numbers of DDDs per 100 bed-days. Consumption of antihypertensive, anticoagulant and antiplatelet agents intended for basic and specific therapy, and secondary prevention of ACVA, equaled 58.0% of the total DDDs' number. Results of the research may act as a background for rational drug prescribing for patients with ACVA.

INTRODUCTION

Acute cerebrovascular accidents (ACVA) and stroke as the most severe manifestation of those have been an important medical and social problem worldwide for many years. Thus, according to the medical statistics data, in 2014 acute stroke, ischemic heart disease and lower respiratory tract infections have been the main reasons for lost years of life due to premature death (WHO, 2014). In Ukraine, the rates of morbidity and mortality from stroke stay consistently high and overweigh those of the majority of European countries (Revenko, 2010; Filipets, 2014). That is why providing adequate medical care of patients with ACVA is extremely important. All the stages of such medical aid are strongly interconnected with pharmaceutical aid. The basis of a high-quality pharmaceutical (hence – medical) aid is the application of clinically and economically effective drugs, namely rational drug application (WHO, 1996). In its turn, rational drug use is considered one of the appropriate pharmacotherapeutic practice and polypragmasy prevention principals (Ministry of Health of Ukraine, 2013). It can be achieved through drug consumption analysis, carried out worldwide (Smuseva *et al*., 2012; Basavaraju and Panchaksharimath, 2016; Hanssens *et al*., 2002; Volodina *et al*., 2011; Sharonjeet Kaur *et al*., 2014; Sagar *et al*., 2015) and in Ukraine (Kotvitska and Lobova, 2015; Levytska and Hromovyk, 2012; Mishchenko and Adonkina, 2015; Yakovleva and Ribka, 2013).

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MATERIALS AND METHODS

Objects of the research

We analyzed inpatient medical records and prescription papers (n=2358) of patients of the neurological department based at one of inpatient hospitals in Lviv. Lviv Regional Clinical Hospital is a general hospital that provides high-quality medical aid for population of Lviv region, other regions of Ukraine and foreigners. The Bed capacity of the hospital equals 1110 and embraces 27 inpatient hospital departments, including neurological department for 75 beds. The study was held in 2015, hospital permission from 10th April 2015 in Minutes No 1062/07.

Type of the research

Our research had retrospective character.

Clinical-epidemiological study was directed on identifying different types of ACVA, their gender and age specifics, range of comorbidities, duration of hospitalization.

Pharmaco-epidemiological study itself was identifying drugs for pharmacological treatment of defined ACVA types and correlation of its duration, sequence with age, types and number of comorbidities.

The methods used in the research

Content analysis consisted in identifying the International Nonproprietary Name (INN) for each drug or accredited name (AN) in case of no INN and ranging them according to the levels of Anatomical Therapeutic Chemical (ATC) Classification System, defining specific weight for each group on different levels.

Retrospective frequency analysis was provided in two directions: we identified both the share of patients who had been prescribed some certain drug and the share of certain drug in the total amount of prescriptions (structure of prescriptions). The drugs were classified in range from the most to the least prescribed ones. For this purpose, we selected inpatient prescription papers (IPPs) in chronological order of patients being hospitalized. We formed the sample of medications as for INN or AN, and indicated the calculated number of prescriptions for each drug from each IPP. Then the drugs were placed in order of decline from the most to the least prescribed ones. The share of each drug in the total structure of prescriptions and the share of patients for whom the certain drugs had been prescribed were calculated. The results of the frequency analysis were represented as a proportion of patients who were prescribed the drug or as a share of drug in the total amount of all prescriptions.

Using ABC analysis (Pareto principle, 80/20 rule), we divided medications from the sample into 3 categories (A, B, and C) according to frequency of prescriptions (hence – their estimated importance of being prescribed) for patients with ACVA. The "A" group includes 10-20% of the total, prescribed in 70-80% of cases. Group "B" includes 20-30% of drugs that were prescribed in 15 - 20% of cases. The rest form group "C".

The rates of consumption were calculated with the help of ATC/DDD and drug utilization (DU) 90% analyses. The defined daily dose (DDD) – the average maintenance dose of the drug when used on its major indication in adults (WHO, 2003) – was calculated. We took the information about the amount of consumed drug (tabs, capsules, vails etc.) from the inpatient prescription paper. Considering the amount of the active ingredient in the defined dosage forms, we counted the total amount of the drug in grams, milligrams, units etc. Afterwards we calculated the number of consumed DDDs as the ratio of the total amount of consumed drug (mg, g etc.) to the value of DDD. Findings were rated from the max number of consumed DDDs to min number of those. In addition, the consumption indicator showing a number of DDDs per 100 bed-days was set. The calculations were performed using the formula as follows: DDDs/100 bed-days = (DDDs x 100) / total number of bed-days. The DU 90% analysis showed number of drugs that owned 90% of consumed DDDs. Each prescribed drug was ranged from max to min value of DDD. The share of each drug in the total amount was defined. The total number of drugs was taken for 100%. We formed two groups of drugs. The first included drugs that make 90% of all consumed DDDs. The rest of the drugs were included into the second group. Generalization of results helped to make the conclusions.

The conflict of the interests in the course of the research was not reported. The Conclusion of Human Research Ethics Committee of Danylo Halytsky Lviv National Medical University is in Minutes No 4, 20th April 2015.

Statistics

Statistical data processing was performed with the help of Statistica 10 Trial software (StatSoft, 2010). The quantitative measures (age, number of comorbidities, and duration of treatment) were compared. For the processed indicators the average value was identified and standard deviation (SD) specified. Normality of data distribution in samples was evaluated by means of Shapiro–Wilk test. Whereas the data distribution differs from the normal, the non-parameter methods were used for their evaluation, the Kolmogorov–Smirnov test in particular. Differences were considered significant when $p<0.05$ (Serhiienko, 2000).

RESULTS AND DISCUSSION

In the analyzed period, 2358 patients had been treated at the neurological department, 300 of them (12.7% of the total) with ACVA. There were 183 male and 117 female patients (correlation 1.6: 1). Age range for male patients was within 18 – 96 years, the average age (m±SD) was 58.2±13.79 years (median score of 57 years, 25% – 51 year, 75% – 68 years). For women the age range was within 18 – 87 years, and the average age was 62.9±15.48 years (median score of 66 years, 25% – 50 years, 75% – 76 years) ($p < 0.001$). Therefore, differences due to age between men and women were significant (fig.1). The frequency of ACVA in

patients of the neurological department, standardized by age and gender is represented on fig.2.

According to the data represented on the fig.2, in both groups ACVA as usual developed in the age of 50 and elder (total 77.6% of cases in men and 76.0% of cases in women). Therewith, ACVA in male patients aged 55 – 59 years was marked 5 times more often than in female patients of the same age. Starting from the age of 65 years, the trend changed to the opposite: the number of ACVA cases was almost twice higher in women. Women in the age of 80 and elder 2.6 times more often suffered from ACVA. Some 50.3% of patients were diagnosed cerebral infarction (names of vascular brain disorders are represented according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (WHO, 2015)), 44.3% – sequelae of cerebrovascular disease, in 8.7% – hemorrhage (intracerebral, subarachnoid etc.). As in some inpatient medical records not 1 but 2 diagnoses were indicated, the total amount of cerebrovascular disorders equals somewhat higher than 100%. Correlation of ischemic strokes to cerebral hemorrhage was 5.8:1, namely, ischemic strokes occurred 5.8 times more often than hemorrhage. Monitoring of comorbidities in patients with ACVA showed those were diagnosed in 96.2% of males and in 97.4% of females. Min amount of comorbidities in male patients equaled 1, max – 12, the average amount of comorbidities was 4.3±2.26 (median score of 4 disorders, 25% – 3 disorders, 75% – 6 disorders) (fig.3).

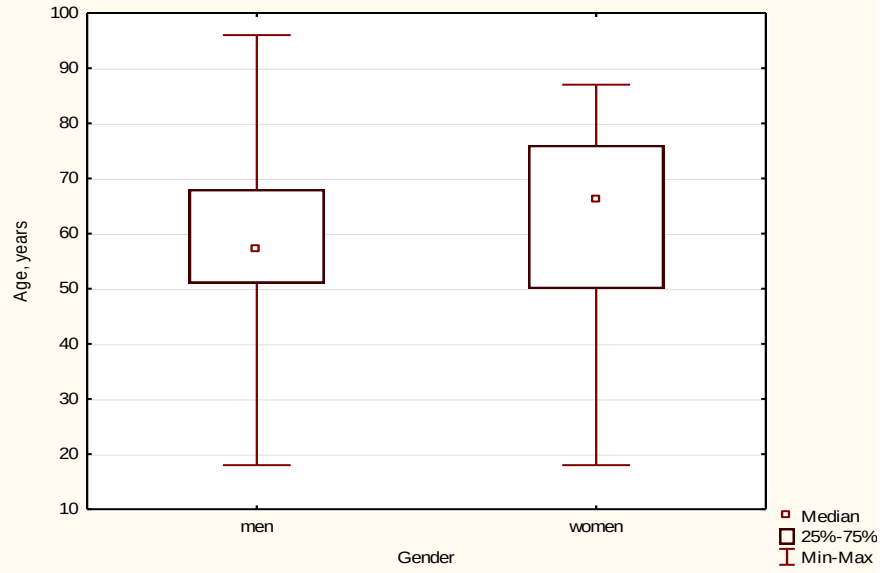

Fig. 1: "Box-and-whisker" plot for patients' gender and age.

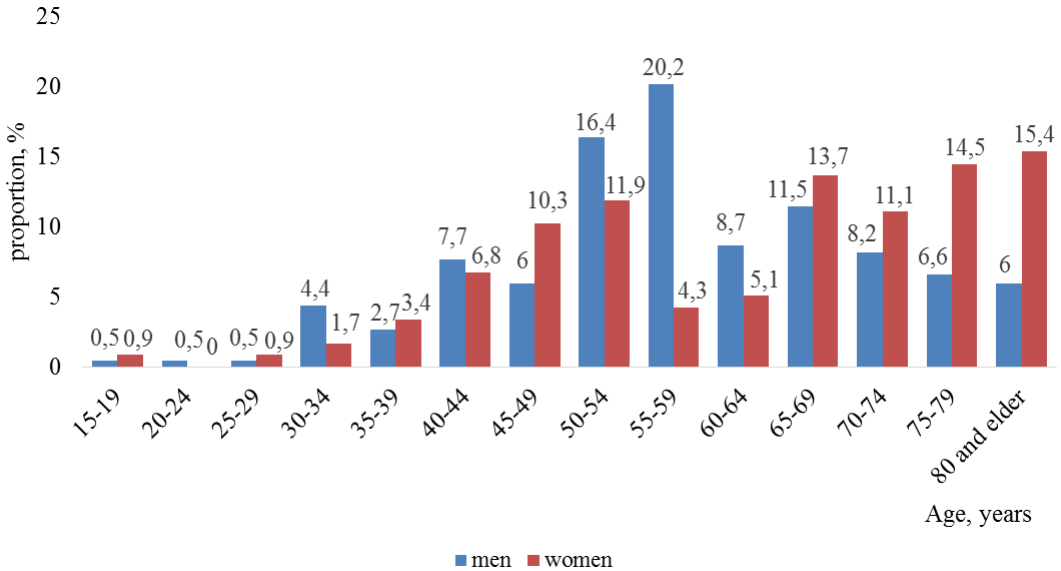

Fig. 2: The frequency of ACVA standardized by age and gender.

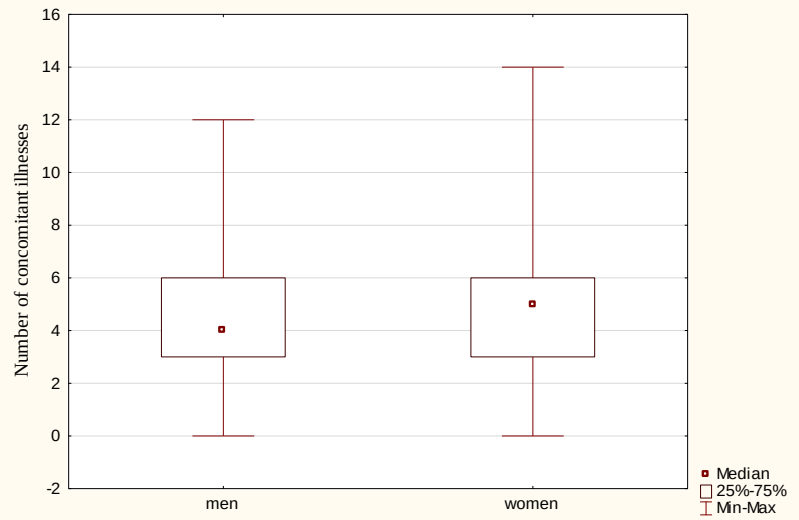

Fig.3. "Box-and-whisker" plot for comorbidities

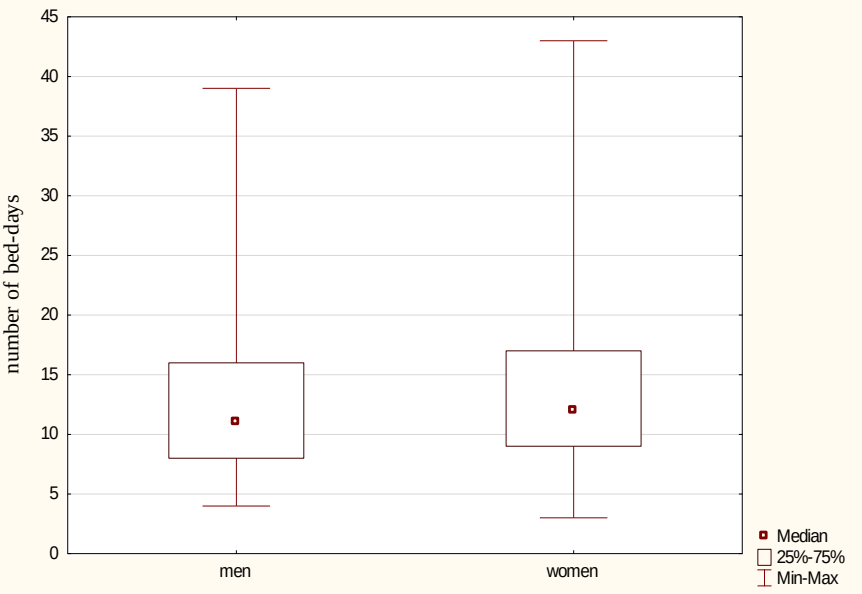

Fig.4. "Box-and-whisker" plot for spent bed-days

For female patients min amount of comorbidities also equaled 1, max – 14, the average amount of comorbidities was 4.5±2.28 (median score of 5 disorders, 25% – 3 disorders, 75% – 6 disorders) ($p > 0.10$), so the research groups of patients did not differ significantly by the number of comorbidities. In the structure of concomitant diseases in patients with ACVA, the leading position belonged to hypertension with the frequency of 82.0% of cases. Bilateral hypertensive retinopathy was diagnosed in 59.7% of patients, heart failure at different stages – in 57.7%, and ischemic heart disease – in 51.3% of patients. For male patients the min duration of hospitalization equaled 4 bed-days, max – 39 bed-days, average duration of hospitalization was 12.7±6.59 bed-days (median score of 11 bed-days, 25% – 8 bed-days, 75% – 16 bed-days) (fig.4). For females, min duration of hospitalization equaled 3 bed-days, max – 43 bed-days, average duration of hospitalization was 13.9±7.55 bed-days (median score of 12 bed-days, 25% – 9 bed-days, 75% – 17 bed-days) ($p > 0.10$), i.e. there was no statistically significant difference between the studied groups.

Content analysis of the IPPs helped to identify 198 drugs according to the INN or AN among 75 subgroups of the third level of ATC classification system. The drugs represented 10 organ-or-system groups of the classification. They were prescribed to the patients for treatment of the main disorder as well as for comorbidities. Among the main organ or system groups of drugs that were used for treatment of ACVA, the max specific weight belonged to the Cardiovascular system group of drugs used for treatment of ACVA (C group) – 29.8%. The specific weight of the N group (Nervous system group), A group (Alimentary tract and metabolism), and B group (Blood and blood forming organs) was

22.2%, 18.2% and 12.1% accordingly. Therefore, almost 83% of drug prescriptions were represented by the four organ or system groups – C, N, A and B.

Prescriptions monitoring in terms of the groups of the third (therapeutic) level (table 1) showed that the max specific weight accounted for B01A group – Antithrombotic agents (6.6%).

The results of frequency analysis (Levytska *et al*., 2014) proved the significance of 8 drugs from the statistical set. Particularly, they were Magnesium sulfas 8.1%, L-lysine aescinat – 7.9%, Potassium chloride – 6.2%, Ipidacrine – 4.1%, Enoxaparin – 3.9%, Cerebrolysin – 3.6%, Atorvastatin – 3.3%, Choline alfoscerate – 2.7%. These same medications were prescribed to 22.0% – 66.7% of patients. For other drugs, the fraction of prescriptions was less than 2%.

ABC-analysis (Levytska *et al*., 2014) showed that 40 drugs (or 20.2% of drug nomenclature) belong to group A, and had been prescribed to patients in 73.9% of cases. Drugs from group B, i.e. 55 names of medications (27.8% of drug nomenclature), had been prescribed in 18.3% of cases. Finally, 103 drugs (52.0% of nomenclature) had been prescribed only in 7.8% of cases.

The further stage of the research was drug consumption analysis on the behalf of ATC/DDD and DU 90% methods (Levytska *et al*., 2014). We calculated the DDD for 141 drug (or 71.2%) of the total count. However, it was not calculated for 6 of 8 mentioned above drugs that possessed high rates of prescriptions (Magnesium sulfas, L-lysine aescinat, Potassium chloride, Ipidacrine, Cerebrolysin, and Choline alfoscerate). It predetermined some underestimation of drug consumption. We discovered that the high rates of consumption were typical for 3 drugs as follows: Atorvastatin (1588 DDDs), Dexamethasone (1386.7 DDDs), and Enoxaparin (1381 DDDs). The significant rates of consumption were also typical for 6 following drugs: Rosuvastatin (685.5 DDDs), Vitaxon (600 DDDs), Acetylsalicylic acid (489 DDDs), Ramipril (452 DDDs), Neurorubine (450 DDDs), and Betahistine (417.3 DDDs). If we take into consideration that mentioned above Vitaxon and Neurorubine, as well as Neuromax and Milgamma (the DDDs of which were 182 and 176 respectively), are the fixed combination preparations of vitamins B_1, B_6, and B_{12}, it turns obvious that vitamin preparations altogether were characterized by considerably high rate of consumed DDDs – 1408 (see next). For 19 drugs the number of DDDs was between 110 (Cormagnesin) and 394 (Cardiomagnyl). The rates of consumption of the other analyzed drugs were of less than 100 DDDs.

The DU 90% analysis showed that 90% of consumed DDDs accounted for 45 drugs. Herewith, for 36 of them an interrelation between the number of consumed DDDs and the share of prescriptions was typical (Atorvastatin, Dexamethasone, Enoxaparin, Rosuvastatin, Vitaxon, Acetylsalicylic acid, Ramipril etc.). However, the drugs like Perindopril arginine, Lisinopril, Amlodipine etc., which belong to group of 90% of consumption, are characterized by the small share of prescriptions (0.12 – 0.28%). Moreover, vice versa, drugs like Nicotinic acid, Warfarin, Quetiapine, Metamizole sodium etc. (which had the share of prescriptions ranging from 0.33 to 1.06%), were not included into group of 90% of consumption.

For the drugs under research, the consumption indicator showing a number of DDDs per 100 bed-days was set. The calculations were performed using the formula as follows: DDDs/100 bed-days = (DDDs x 100) / total number of bed-days (n=3942). The drugs like Atorvastatin, Dexamethasone, and Enoxaparin were characterized by high numbers of DDDs per 100 bed-days (40.3, 35.2, and 35.0 accordingly). For Rosuvastatin, Vitaxon, Acetylsalicylic acid, Ramipril, Neurorubine, Betahistine and Cardiomagnyl the DDDs/100 bed-days indicators have the following rates: 17.4, 15.2, 12.4, 11.5, 11.4, 10.6 and 10.0 accordingly. For 46 drugs, the DDDs/100 bed-days indicator ranged from 1.0 to 9.0, for the rest drugs this indicator's value was less than 1.0.

Table 1: The share of separate therapeutic subgroups, prescribed for treatment of ACVA.

Name of the therapeutic subgroup	ATC code	Amount of drugs by INN or AN	
		Abs.	%*
1. Antithrombotic agents	B01A	13	6.6
2. Psychostimulants, agents used for Attention deficit hyperactivity disorder (ADHD) and nootropics	N06B	12	6.1
3. Angiotensin-converting enzyme (ACE) inhibitors, combinations	C09B	8	4.0
4. Other cardiac preparations	C01E	7	3.5
5. Anti-inflammatory and antirheumatic products	M01A	6	3.0
6. Vitamin B1, plain and in combination with vitamin B6 and B12	A11D	6	3.0
7. Beta blocking agents	C07A	5	2.5
8. ACE inhibitors	C09A	5	2.5
9. Antipsychotics	N05A	5	2.5
10. Antidepressants	N06A	5	2.5
11. Intravenous solution additives	B05X	5	2.5
Total:		77	38.7
Other 64 therapeutic subgroups		121	61.3

* - share of the total amount of drugs (n=198)

Table 2: Distribution of Atorvastatin prescriptions by the trade names for ACVA patients.

Trade name of the drug, manufacturer	Number of consumed		
	tab.	mg	DDDs
Atoris, tab. 10 mg N 30, KRKA, Slovenia	46	460	23
Atoris, tab. 20 mg N 30, KRKA, Slovenia	348	6960	348
Atoris, tab. 30 mg N 30, KRKA, Slovenia	23	690	34.5
Atoris, tab. 40 mg N 30, KRKA, Slovenia	64	2560	128
Atoris, tab. 60 mg N 30, KRKA, Slovenia	73	4380	219
Total Atoris			**752.5**
Atorvastatin, tab. 10 mg N 30, Pfizer, USA	43	430	21.5
Atorvastatin, tab. 20 mg N 30, Pfizer, USA	46	920	46
Total Atorvastatin			**67.5**
Atorvastatin-Teva, tab. 40 mg N 30, Teva, Israel	27	1080	54
Atorvastatin-Teva, tab. 80 mg N 30, Teva, Israel	42	3360	168
Total Atorvastatin-Teva			**222**
Tolevas, tab. e/c 20 mg N 30, Nobel, Turkey	49	980	49
Tolevas, tab. e/c 40 mg N 30, Nobel, Turkey	28	1120	56
Total Tolevas			**105**
Tulip, tab. e/c 20 mg N 30, Lek, Slovenia	16	320	16
Total Tulip			**16**
Livostor, tab. e/c 10 mg N 30, Kyiv Vitamin Factory, Ukraine	27	270	13.5
Livostor, tab. e/c 20 mg N 30, Kyiv Vitamin Factory, Ukraine	72	1440	72
Livostor, tab. e/c 40 mg N 30, Kyiv Vitamin Factory, Ukraine	63	2520	126
Total Livostor			**211,5**
Lipodemin, tab. 10 mg N 30, Propharma International, Malta	24	240	12
Lipodemin, tab. 20 mg N 30, Propharma International, Malta	11	220	11
Total Lipodemin			**23**
Liprimar, tab. e/c 20 mg N 30, Pfizer, USA	8	160	8
Liprimar, tab. e/c 40 mg N 30, Pfizer, USA	30	1200	60
Liprimar, tab. e/c 80 mg N 30, Pfizer, USA	20	1600	80
Total Liprimar			**148**
Storvas, tab. e/c 10 mg N 30, Ranbaxy, India	21	210	10.5
Storvas, tab. e/c 20 mg N 30, Ranbaxy, India	12	240	12
Total Storvas			**22,5**
Amvastan, tab. e/c 20 mg, Rottapharm, Germany	20	400	20
Total Amvastan			**20**
Total:			**1588**

The results of drugs consumption analysis for selected trade names are represented by the example of Atorvastatin that is characterized by max number of consumed DDDs (Table 2). The DDD for this drug is 20 mg if taken per os (WHO, 2016). Max drug consumption was typical for different dosage of Atoris, KRKA (Slovenia), i.e. 752.5 DDDs. Taking into consideration current approaches to treatment of ACVA, we analyzed drug consumption in the aspect of common groups of preparations that are used for basic and specific therapy, and for secondary prevention of the disorder. These are antihypertensive drugs, anticoagulants, antiplatelet agents, and statins. In general, antihypertensive agents were prescribed to 62% of patients, statins – to 38%, anticoagulants – in 43% of cases, and antiplatelet agents – to 46.3% of patients (table 3).

Table 3: Results of the consumption analysis for separate groups of drugs.

Name of the group	Share of patients who were prescribed the drugs, %	Total number of DDDs	DDDs/100 bed-days
Antihypertensive drugs	62.0	3261.7	82.7
Statins	38.0	2312.2	58.7
Anticoagulants	43.0	1520.4	38.6
Antiplatelet drugs	46.3	1301.0	33.0

Consumption of the mentioned groups of drugs was 58% of DDDs. According to the valid in Ukraine medical-and-technological documents that regulate the provision of medical care to patients with ACAV (Ministry of Health of Ukraine, 2012), there are several separate indicators of medical care quality. This, in particular, is prescribing of Acetylsalicylic acid (antiplatelet agent) within 48 hours of the onset of stroke symptoms, prescribing of antithrombotic agents (antiplatelet drugs or anticoagulants) and lipid-lowering pharmacotherapy (statins) at the time of discharge from the hospital (Ministry of Health of Ukraine, 2012). Considering this, we believe, optimization of prescribing the mentioned groups of drugs for such patients is advisable. As for the vitamin B group, analyses like frequency of prescribing, number of consumed DDDs, and DDDs/100 bed-days show that in the investigated inpatient hospital these drugs were prescribed rather often (particularly, fixed combinations of vitamin B complex containing Thiamine chloride (B1), Pyridoxine hydrochloride (B6) and Cyanocobalamin (B12)) (table 4). Besides, a considerable number of consumed DDDs belong to them.

It is well known that group B vitamins decrease levels of homocysteine – one of the risk factors for cardiovascular disorders. The question of their use or non-use for patients with ACVA remains open and controversial because the results of many researches do not give a clear answer about their benefits, harm or futility in treatment of ACVA (Meng *et al*., 2010; Yan Ji *et al*., 2013). However, in the native Ukrainian adopted evidence-

based clinical guidelines "Recommendations on managing patients with ischemic stroke and transient ischemic attack" it is mentioned that homocysteine-lowering vitamins (Folic acid, Pyridoxine hydrochloride and Cyanocobalamin) do not decrease risk of recurrent stroke and can increase frequency of vascular events; although at present time further studies proceed (Ministry of Health of Ukraine, 2012). That is why we consider investigation of prescribing vitamin preparations to patients with ACVA a curious topic for further research.

Table 4: Results of vitamin B consumption analysis.

Name of the drug	Share of patients who were prescribed the drugs, %	Total number of DDDs	DDDs/ 100 bed-days
Fixed combination of vitamins B_1, B_6 and/or B_{12}	30.0	1408	35.7
Thiamine chloride (B_1)	5.7	121	3.1
Pyridoxine hydrochloride (B_6)	2.3	13.1	0.3

CONCLUSIONS

1 The results of our study prove the tendency to occurrence of ACVA in patients aged 50 and over with the vast prevalence of cerebral infarction over hemorrhage. The disorder is interlinked with one or few comorbidities, especially hypertension. Therefore, we believe, increasing awareness of ACVA and problems of its medical treatment (including pharmaco-economical aspect) among specialists and risk-groups of patients is an important issue directed on the disease prevention, especially in Ukraine. This might be provided by means of specially designed workshops and distribution of important information on social media and networks.

2 As far as we found a number of consumption problems and cases of inappropriate drug prescribing, the results of our research should act as a background for prescribing rational pharmacotherapy to patients with ACVA, optimization of both pharmacotherapy in some particular cases, and the process of its quality regulation. We believe, the data developed in this research should be taken into consideration by the current health care system of Ukraine and included into State programs on quality of pharmacotherapy improvement.

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