International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2016): 79.57 | Impact Factor (2015): 6.391

Substantiation of Rational Choice of Statin Therapy in Ukraine

Oksana Tryhubchak

JSC Farmak, R&D Department, Kiev, Ukraine

Abstract: ***This study was conducted using marketing, pharmacoeconomical research of statins in Ukraine. It was found that the largest number of people taking statins use atorvastatin (51%), simvastatin (31%), rosuvastatin (16%), lovastatin (2%). By costs minimization, cost-effectiveness and cost-utility analysis it was chose the least costly statins in Ukraine. We found differences in seven Issues of State Formulary of Drugs in Ukraine for the statin groups. The well-founded pharmacoeconomic benefits of rosuvastatin 10 mg included reducing the risk of morbidity and mortality, for atorvasatin 10 mg the reducing of low-density lipoprotein***

Keywords: statin, rational choice, market analysis, pharmacoeconomics, pharmacoepidemiology

1. Introduction

Ukraine has second position in the world by death rate/1000 (14.46%) and mortality from coronary heart disease. Thus, 50.26 % (329 thousand) Ukrainians died from cardiovascular disease in 2014 [1]. These depressing statistics of mortality from cardiovascular diseases in Ukraine depend on many factors. One of them is the lack of proper understanding by the country's doctors, patients and, most importantly, the leadership of health, of the potential role of statins in reducing mortality in at least some patients with atherosclerotic disease and in healthy individuals that have major risk factors - high cholesterol and arterial hypertension. An increase in the plasma concentration of triglycerides is an established risk factor for cardiovascular disease [2], most likely because the cholesterol content of the triglyceride-rich lipoproteins or remnant cholesterol seems to be causally associated with ischemic heart disease [3].

The basis of that conclusion is historical research on the use of statins in primary and secondary prevention of atherosclerotic disease which proved in a most convincing way the possibility of substantial and significant reduction in total mortality (from all causes) and from cardiovascular diseases [4].

Statin is a structural analog of HMG-CoA enzyme and is effective in reducing low-density lipoprotein. It shows its pharmaceutical action by inhibiting the key enzyme involved in cholesterol synthesis, which is called HMG-CoA reductase. Therefore, statin is referred to as HMG-CoA reductase inhibitors. Reducing elevated levels of atherogenic cholesterol (non–high-density lipoprotein cholesterol and low-density lipoprotein cholesterol) reduces the risk for atherosclerotic cardiovascular disease [5]. Statin has been associated with a beneficial effect on cardiovascular morbidity and mortality. It has significant anti-inflammatory and plaque-stabilizing effects. Its other effects include decreased oxidative stress and vascular inflammation associated with increased atherosclerotic lesions. Some of the currently available statins are atorvastatin, lovastatin, rosuvastatin, and simvastatin [6].

Statins are not only recognized and indisputable for the treatment and prevention of atherosclerosis and related acute and chronic diseases, but also for the most convenience for patients (taking them once, occasionally twice daily). They are also well tolerated compared to all lipid-lowering agents [7,8].

Technavio's analysts forecast the global statin market to decline at a CAGR of 7.50 % over the period 2014-2019 [9]. Statin products are very high margin, so if a statin generates around 20% of a company’s sales, it is likely to contribute 30% to its profits. But pharmaceutical companies are facing increasing competition from cheaper generic statins. Around 80% of a branded drug’s sales quickly evaporate when faced with generic competition [10].

National Lipid Association developed recommendations by a diverse panel of experts who examined the evidence base and provided recommendations [11]. Current guidelines for the treatment of cholesterol to reduce cardiovascular risk recommend that the following four groups of patients will benefit from moderate- or high-intensity statin therapy [12]:

1) Individuals with clinical atherosclerotic cardiovascular disease.
2) Individuals with primary elevations of low-density lipoprotein ≥ 190 mg/dL.
3) Individuals 40 to 75 years of age with diabetes and a low-density lipoprotein 70 to 189 mg/dL without clinical atherosclerotic cardiovascular disease.
4) Individuals without clinical atherosclerotic cardiovascular disease or diabetes who are 40 to 75 years of age with low-density lipoprotein 70 to 189 mg/dL and a 10-year atherosclerotic cardiovascular disease risk of 7.5% or higher.

But there is room for better low-density lipoprotein cholesterol management among high-risk cardiovascular disease patients to reduce their overall cardiovascular risk [13].

Very often doctors have difficulty in choosing the drug from available statins. Therefore, the aim of the research was to establish a rational choice of drug for statin therapy cardiovascular disease for adults.

2. Literature Survey

During many years it was thought that of myocardial infarction associated with the progressive growth of plaque that narrows the lumen so that almost completely covers the bloodstream, and lipid-lowering therapy was carried out in the hope that by lowering lipid levels can achieve regression of coronary atherosclerosis. This position is reflected in the design of the first so-called statins angiographic studies: MARS [14], CCAIT [15], MAAS [16], PLAC1 [17]. They were made to assess the impact of statins on the progression of coronary atherosclerosis and characterized by a limited number of patients included and the relatively short duration. The results of these studies were paradoxical. Apart from isolated cases of plaques statin therapy compared to the control group average was accompanied by a small but significant slowing of the progression of coronary artery stenosis, but small (0,03-0,06 mm absolute) difference in the changes in the diameter of the vessel lumen could not explain the significant (by 24-42%) reduction in cardiac events.

Prospective placebo-controlled clinical trials using statins conducted in the mid 90s, differed from previous angiographic study a large number of participants (several thousand), duration (56 years) and were intended to reduce clinical endpoints (analyzed event, which is judged on the effectiveness of or other interference), coronary events (myocardial infarction, coronary death) and even deaths from all causes.

These results were impressive and this changed the existing idea of the possibilities lipid-lowering therapy, a significant (25-35%) reduction in low density lipoprotein cholesterol during treatment with statins (simvastatin, pravastatin, lovastatin) was accompanied by a significant decrease in fatal and non-fatal cardiac events without increase or decrease of total mortality. Favorable effects of statins on clinical endpoints were obtained in patients with coronary artery disease (4S [18], CARE [19], LIPID [20]) and in patients without evidence of coronary artery disease (WOSCOPS [21], AFCAPS / TexCAPS [22]), not only in patients with severe hypercholesterolemia, but at relatively low levels of low-density lipoprotein cholesterol.

Reducing not only the heart but also total mortality on a background statin therapy prolonged, demonstrated in prospective platsebo controlled clinical trials finally dispelled all doubts about the safety of lipid-lowering drugs statins in general and in particular. Based on the results of these studies, the presence of hyperlipidemia statins not only in patients with coronary artery disease, but people and no signs of coronary artery disease but with high risk of cardiovascular events should be considered not only justified but mandatory [23,24].

General and detailed guidelines for the clinical evaluation and management of lipid disorders have stimulated generation of similar recommendations from all over the world, particularly Europe, Canada, Australia and Asia [25].
Long-term therapy with statins (for at least one year) has been shown to reduce the risk of heart attack, stroke, and all-cause mortality in patients with and without established coronary heart disease. Eighteen studies (14,303 patients) showed that the risk of unstable angina was reduced by about 25% at four months following acute coronary syndrome [26]. All-cause mortality was reduced by statins (OR 0.86, 95% CI 0.79 to 0.94); as was combined fatal and non-fatal cardiovascular disease RR 0.75 (95% CI 0.70 to 0.81), combined fatal and non-fatal coronary heart disease events RR 0.73 (95% CI 0.67 to 0.80) and combined fatal and non-fatal stroke (RR 0.78, 95% CI 0.68 to 0.89). Reduction of revascularisation rates (RR 0.62, 95% CI 0.54 to 0.72) was also seen [27].

To reduce all-cause mortality patients who have never had coronary heart disease have shown pravastatin (high-risk patients), simvastatin (mixed populations), rosuvastatin (patients with elevated C-reactive protein). Patients with coronary heart disease would take atorvastatin (post myocardial infarction), pravastatin, simvastatin. To reduce cardiovascular mortality for patients who have never had coronary heart disease is recommended pravastatin, simvastatin; for patients with coronary heart disease – simvastatin, atorvastatin. To reduce coronary heart disease events patients who have never had coronary heart disease have shown atorvastatin (high-risk patients, patients with diabetes), lovastatin (average-risk patients), pravastatin (high-risk patients), simvastatin (mixed populations), rosuvastatin (patients with elevated C-reactive protein); patients with coronary heart disease – atorvastatin, simvastatin, pravastatin; patients after percutaneous transluminal coronary angioplasty – fluvastatin, pravastatin [28].

Pravastatin, atorvastatin, simvastatin trials showed a reduction in subsequent serious vascular events (OR 0.74, 95% CI 0.67 to 0.82) [29].

Studies of the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 11, 2013), MEDLINE (1966 to December Week 2 2013), EMBASE (1980 to December Week 2 2013), Web of Science (1899 to December Week 2 2013) and BIOSIS Previews (1969 to December Week 2 2013) show that atorvastatin decreases blood total cholesterol and low-density lipoprotein cholesterol in a linear dose-related manner over the commonly prescribed dose range. New findings include that atorvastatin is more than three-fold less potent than rosuvastatin, and that the cholesterol-lowering effects of atorvastatin are greater in females than in males and greater in non-familial than in familial hypercholesterolaemia. This review update does not provide a good estimate of the incidence of harms associated with atorvastatin because included trials were of short duration and adverse effects were not reported in 37% of placebo-controlled trials [30].

The effects of atorvastatin at 20, 40, and 80 mg/day on plasma lipoprotein subspecies were examined in a randomized, placebo-controlled fashion over 36 weeks in 97 patients with coronary heart disease with low-density lipoprotein (low-density lipoprotein) cholesterol levels of >130 mg/dl and compared directly with the effects of fluvastatin (n = 28), pravastatin (n = 22), lovastatin (n = 24),

and simvastatin (n = 25). The effects of placebo and 40 mg/day of each statin were also examined in subjects with coronary heart disease with subjects in the fasting state and in the fed state 4 hours after a meal rich in saturated fat and cholesterol and compared with results in age- and gender-matched control subjects. At all doses tested in the fasting and fed states, atorvastatin was significantly ($p < 0.01$) more effective in lowering low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol than all other statins, and significantly ($p < 0.05$) more effective than all statins, except for simvastatin, in lowering triglyceride and remnant lipoprotein cholesterol. At 40 mg/day in the fasting state, atorvastatin was significantly ($p < 0.01$) more effective than all statins, except for lovastatin and simvastatin, in lowering cholesterol levels in small low-density lipoprotein, and was significantly ($p < 0.05$) more effective than all statins, except for simvastatin, in increasing cholesterol in large high-density lipoprotein and in lowering low-density lipoprotein particle numbers. The data indicate that atorvastatin was the most effective statin tested in lowering cholesterol in low-density lipoprotein, non-high-density lipoprotein, and remnant lipoprotein in the fasting and fed states, and getting patients with coronary heart disease to established goals, with fluvastatin, pravastatin, lovastatin, and simvastatin having about 33%, 50%, 60%, and 85% of the efficacy of atorvastatin, respectively, at the same dose in the same patients [31].

The Myocardial Ischemia Reduction with Acute Cholesterol Lowering (MIRACL) Trial tested the hypothesis that intensive lowering of cholesterol with atorvastatin (80 mg/day) initiated 24-96 h after an acute coronary syndrome would, over 4 months, reduce the incidence of the composite endpoint of death, nonfatal infarction, resuscitated cardiac arrest, and recurrent symptomatic myocardial ischemia with new objective symptoms requiring emergency rehospitalization. This primary composite endpoint was reduced from 17.4% to 14.8% ($P = 0.048$) among the 3086 patients enrolled. The results of MIRACL suggest that patients with acute coronary syndromes should begin to receive this treatment before leaving hospital, irrespective of baseline levels of low-density lipoprotein-cholesterol [32].

For patients with acute coronary syndrome, lipid-lowering therapy with atorvastatin, 80 mg/d, reduces recurrent ischemic events in the first 16 weeks, mostly recurrent symptomatic ischemia requiring rehospitalization [33].

The GALAXY Program is a series of clinical studies investigating the efficacy and tolerability of rosuvastatin in line with the hypothesis that the statin with the greatest efficacy for improving the atherogenic lipid profile and beneficially modifying inflammatory markers will also slow progression of atherosclerosis and improve cardiovascular outcomes. Completed studies report that rosuvastatin is more effective than comparator statins in reducing low-density lipoprotein cholesterol, improving the lipid profile and enabling patients to achieve lipid goals, including revised, more stringent goals, even in high-risk patients. Studies have also reported that rosuvastatin can arrest and even regress atherosclerosis. Ongoing outcomes studies will determine whether these beneficial effects of rosuvastatin translate into reduced morbidity and mortality [34].

Evidence suggests that rosuvastatin has the most potent per milligram low-density lipoprotein lowering effect but with appropriate dosage adjustments different statins can provide equivalent low-density lipoprotein reductions. Data suggests similar effects on high-density lipoprotein, triglyceride and C-reactive protein with rosuvastatin compared with other statins. Based on the identified literature, there is no significant difference in rates of adverse events between rosuvastatin and other statins [35].

The STELLAR (Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin) study found that after six weeks of treatment, rosuvastatin resulted in significantly greater low-density lipoprotein cholesterol reductions dose for dose compared with other statins. Analyses showed that rosuvastatin 10 to 80 mg reduced low-density lipoprotein cholesterol by a mean of 8.2 % more than atorvastatin 10 to 80 mg, 26 % more than pravastatin 10 to 40 mg, and 12% to 18 % more than simvastatin 10 to 80 mg (all $p < 0.001$). Rosuvastatin 10mg led to an average 46 % low-density lipoprotein reduction, atorvastatin 10mg - 37%, simvastatin 40mg – 39 %, pravastatin 40 mg – 30 % [36].

Rosuvastatin 10 to 40 mg was more efficacious in improving the lipid profile of patients with hypercholesterolemia than milligram-equivalent doses of atorvastatin and milligram-equivalent or higher doses of simvastatin and pravastatin [37].

The total blood total cholesterol, low-density lipoprotein cholesterol and non- high-density lipoprotein-cholesterol-lowering effect of rosuvastatin was linearly dependent on dose. Rosuvastatin log dose-response data were linear over the commonly prescribed dose range. Based on an informal comparison with atorvastatin, this represents a three-fold greater potency. The Cochrane Central Register of Controlled Trials (CENTRAL) Issue 10 of 12, 2014 in The Cochrane Library, MEDLINE (1946 to October week 5 2014), EMBASE (1980 to 2014 week 44), Web of Science Core Collection (1970 to 5 November 2014) and BIOSIS Citation Index (1969 to 31 October 2014) did not provide a good estimate of the incidence of harms associated with rosuvastatin because of the short duration of the trials and the lack of reporting of adverse effects in 44% of the placebo-controlled trials [38].

In middle-aged adults with Framingham Risk Score of less than 10% and evidence of subclinical atherosclerosis, rosuvastatin resulted in statistically significant reductions in the rate of progression of maximum constraint induced movement therapy over 2 years vs placebo [39].

Rosuvastatin significantly reduced the incidence of major cardiovascular events in apparently healthy persons without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels [40].

Rosuvastatin 10 or 20 mg is an effective and safe therapeutic option for high-risk patients to achieve their lipid and apolipoprotein targets [41].

Significant improvement in low-density lipoprotein cholesterol goal achievement was found for patients who switched to rosuvastatin 10 mg, compared with patients who

remained on atorvastatin 10 mg (86% vs 80%, P <0.05), simvastatin 20 mg (86% vs 72%, P <0.0001), and pravastatin 40 mg (88% vs 66%, P <0.0001), and between patients switched to rosuvastatin 20 mg and those who remained on atorvastatin 20 mg (90% vs 84%, P<0.01) [42].

Confirmed impact of rosuvastatin on atherosclerotic coronary and carotid arteries, and shown its ability to cause mild regression of coronary atherosclerosis in studies ASTEROID, METEOR. Admittedly, rosuvastatin from other statins characterized their pharmacological properties, high lipid-lowering activity and clinical efficacy, especially in patients at high risk of cardiovascular complications, making it promising in the prevention of organ lesions in patients with atherosclerosis at all stages of the process [43,44].

Pravastatin reduced the risk of stroke over a wide range of lipid values among patients with documented coronary disease. This effect was due to a reduction in nonfatal nonhemorrhagic strokes [45].

Numerous clinical trials have demonstrated that statins are effective in lowering low-density lipoprotein cholesterol and reducing cardiovascular risk in people with dyslipidemia. However, the most effective treatments should target all of the key atherogenic features, rather than low-density lipoprotein cholesterol alone. Pitavastatin is a new member of the statin class whose distinct pharmacological features translate into a broad spectrum of action on both apoB-containing and apoA1-containing lipoprotein components of the atherogenic lipid profile. The efficacy and safety of this statin has been demonstrated by a large clinical development programme conducted both in Japanese and Caucasian populations [46].

Results from the 5-year LIVES extension study (N=6,582) showed that long-term treatment with pitavastatin was well tolerated and that the reduction in low-density lipoprotein cholesterol achieved after 104 weeks was maintained for the duration of treatment, whereas levels of high-density lipoprotein-cholesterol continued to rise. Importantly, multivariate analysis of the 5-year data showed that, in addition to advanced age (65 years), male gender, hypertension, diabetes, and a history of ischemic heart disease, on-treatment levels of high-density lipoprotein-cholesterol and low-density lipoprotein cholesterol were significant predictors for cardiovascular and cerebrovascular risk. In this study, the greatest reduction in cardiovascular and cerebrovascular risk was achieved by patients achieving both their low-density lipoprotein cholesterol and high-density lipoprotein-cholesterol targets. Overall, results from the LIVES study show that pitavastatin is well tolerated and effectively modifies atherogenic lipid profiles, thereby reducing cardiovascular and cerebrovascular risk in Japanese patients with hypercholesterolemia. Pitavastatin's ability to significantly and continually increase high-density lipoprotein-cholesterol levels over time suggests a particular benefit for patients with low baseline levels of high-density lipoprotein-cholesterol and/or those that fail to increase their high-density lipoprotein-cholesterol levels using alternative statins [47].

Based on the Cochrane Library Clinical statins the most effectiveness reduce level of low-density lipoprotein, while the action is dose-dependent. Each doubling the dose of statins results in an additional reduction in low-density lipoprotein cholesterol by 6% ("six percent rule").

Statin effects on aggression differed by sex and age: Statins generally decreased aggression in men; and generally increased aggression in women. Both findings were selectively prominent in participants with low baseline aggression – bearing lower change-variance, rendering an effect more readily evident [48].

However, there are a number of risks associated with statin therapy such as elevated blood sugar and enzyme levels, memory impairment, myopathy, rhabdomyolysis and congenital abnormalities. The diabetes risk should be taken into account only if statin therapy is considered for patients at low cardiovascular risk. The risk of diabetes mellitus was found to be minor when compared to cardiovascular benefits. Cognitive impairment such as memory loss was found from a high dose use of statins and resolves on discontinuation of therapy. In statin therapy, muscle toxicity is rare, however creatine kinase levels should be monitored. It is advisable to avoid statins during pregnancy. Finally, overall benefits of statin therapy overcome the risks [49].

3. Methods / Approach

The study analyzed the product range used by the State Register of Medicines Ukraine [50], which includes all registered drugs. The study used data for March 2016. We analyzed the assortment of statin drugs by active ingredients, dosage forms, manufacturer's countries and companies.

Pricing policy of pharmaceutical companies in the domestic market is characterized by changing of liquidity ratio (Rliq), adequacy solvency ratio (Ras) and availability ratio (Ra) [51] for study medicines in the period from January to February 2016 [52].

Costs and benefits depend on the choice of distribution channel. If the company takes over the functions of sales, then it covers the costs involved, but all profits belong to it. If it uses external channels, the costs and profits are distributed among all the participants in the sales channel. Therefore, pharmaceutical companies need to evaluate the benefits and choose an appropriate alternative. Length of sales channel determines the number of intermediaries through which drugs pass on the way from producer to consumer. How many offerings there are in a single product line – that is, whether the product line is broad or narrow – is called line depth. The level's sales channel is any intermediary that performs a particular job to promote drugs to the consumer. Line breadth is a function of how many different, or distinct, product lines a company has. The line breadth of the distribution channel or method of selling drugs, determines the number of independent participants at each level of the channel [53].

In the article we collected information on study drugs based on the Cochrane Library Clinical [54]. To select rational statin for treatment we used pharmacoeconomical analysis such as costs-minimization, cost-effectiveness and cost-utility [51].

In order to choose the least expensive drug with the same proven therapeutic effectiveness we use costs minimization analysis.

Cost effectiveness analysis involves comparing a value (in monetary terms) and efficiency of treatment (direct and indirect clinical effects: changes in physiological, biochemical and physical parameters of the patient). This analysis allows for the assessment of price performance, in particular to evaluate unit cost effectiveness of treatment. The end result is not determined by the cheapest method of treating disease, but optimal performance and the cost. The cost effectiveness analysis depends on the availability of clinical results of sufficient reliability (reliable ways of obtaining information and the possibility of extrapolating the obtained clinical results for use in new conditions), the presence of significant difference in performance of compared treatments and use of the same units of performance measurement. The indicators of the effectiveness of treatment or drugs may be direct clinical effects: changes in physiological, biochemical, physical and other indicators of the patient (blood pressure, hemoglobin levels, the severity of symptoms (pain), extension of life expectancy); indirect clinical effects (reduced frequency of complications, reduced number of repeat hospitalizations); changes in health indicators in studied groups of patients (mortality, survival, life expectancy, etc.) changes in quality of life. The objective of cost effectiveness analysis is to determine optimum performance and cost of treatment.

With cost utility analysis it is possible to compare the cost of treatment in terms of money and its efficiency in terms of utility - treatment outcomes, expressed in terms of quality of life. Indicator utility is often expressed as QALY (quality adjusted life year - number of quality years of life, due to patient treatment), but you can use the indicator utility, which is determined by other suitable techniques in medicine. This method takes into account not only the achievement of certain positive clinical effects but also a favor of the medical intervention on a patient [55].

For calculations, we took total results of systematic reviews on the effect of statins on the incidence of morbidity and mortality.

To calculate costs we used weighted average retail prices of medicines in Ukraine in February 2016 [52]. We calculated the per-package cost for each drug for 1 patient for 1 month of the treatment.

On the basis of pharmacoepydemiological and pharmacoeconomical calculations for the implementation of formulary system in Ukraine since 2009 was compiled State Formulary of Drugs and was recommended for use. A structure of the Formulary also includes statin drugs. We analyzed seven government-issued formularies of drugs in Ukraine (2009-2015 years) for the purpose of comparative evaluation of government recommendations on the drugs with statin [56].

4. Results / Discussion

4.1 Marketing research

In 2016 in Ukraine according to the State Register of Medicinal Products of Ukraine are registered 252 statins. The largest number take drugs based on the active ingredient atorvastatin (percentage is 51% in Ukraine), followed is simvastatin 31%, rosuvastatin – 16% and least amount of drug with lovastatin – only 2%. Dominant dosage form is tablet coated with a cover film. Maybe it is due to the fact that consumers find this form easier to use compared to powder (table 1).

Table 1: Dosage forms of lipid-lowering drugs

Active ingredient	Tablet coated a cover film	Powder
simvastatin	74	4
atorvastatin	125	4
rosuvastatin	40	0
lovastatin	2	3

Intensive imports lipid-lowering drugs from these countries: in the first place - India with 19%; the second - the drugs' domestic production in Ukraine 17%; the third - Slovenia 11%; 8% are imported from the Czech Republic, another 7% are drugs from China and Hungary, and only 5% imports from Germany to Ukraine (fig. 1).

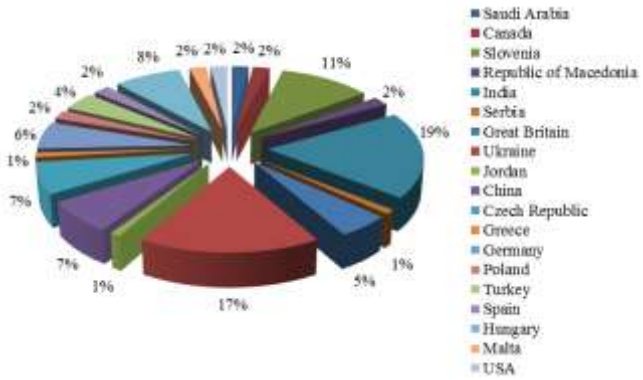

Figure 1: Distribution of lipid-lowering drugs, depending on the country

The share of domestic lipid-lowering drugs on the market is 17%. This share is from 7 manufacturers, of which three are the undisputed leaders: Darnitsa, Farmex and Kusum Pharm Group, holding 25% each. Following are Kievmedpreparat (11%) and Farmak (6%).

The largest share of lipid-lowering drugs is imported from India. Most likely it is due to a large non-solvency of Ukraine's population, as most of these drugs have reasonable prices. The second position after the leader takes Slovenia with 13%, following the Czech Republic - 10%, the Republic Macedonia - 8%, Serbia - 7%, Greek - 6%, Jordan - 5%, per 3% Germany, UK, Saudi Arabia and others.

The price of lipid-lowering drugs is increasing, and this directly affects the economic well-being of the population as lipid-lowering agents are not cheap drugs.

For a detailed analysis of price conjuncture, one can use indicators such as liquidity ratio (Rliq), solvency adequacy ratio (Ras) and availability ratio (Ra).

The liquidity ratio among simvastatin drugs is the lowest for Zocor forte (tab. coated a cover 40 mg №14, Merck Sharp & Dohme Idea, Switzerland) – 0.015, the highest for Vazostat-Zdorovye (tab. coated a cover 40 mg №30, Zdorovye, Ukraine) – 0.211. Among lovastatin drugs the liquidity ration for Lovastatin (tab. 20 mg №30, Kievmedpreparat, Ukraine) – 0.163. Among atorvastatin drugs the worst liquidity ratio is for Caduet 5/10 (tab. coated a cover №30, Pfizer Inc., USA) – 0.002, the highest for Atormac (tab. coated a cover 10 mg №10, Macleods Pharmaceuticals Ltd., India) – 0.562. Among rosuvastatin drugs, the lowest liquidity is for Rosart (tab. coated a cover film 5 mg №30, Actavis, Iceland) – 0.003, and the highest is for Rosart (tab. coated a cover film 40 mg №30, Actavis, Iceland) – 0.210.

Consequently, fluctuations in the price of medicines do not pass the limits of 50%, indicating a slight difference in prices for statins of different wholesalers.

By analyze adequacy solvency ratio we obtained the following data: among drugs simvastatin it is the lowest for Zocor forte (tab. coated a cover 40 mg №14, Merck Sharp & Dohme Idea, Switzerland) – 0.032, the highest - Vasilip (tab. coated a cover film 20 mg №84, KRKA, Slovenia) – 0.721; among drugs lovastatin for Lovastatin (tab. 20 mg №30, Kievmedpreparat, Ukraine) – 0.220; among drugs atorvastatin the lowest is for Atormac (tab. coated a cover 20 mg №10, Macleods Pharmaceuticals Ltd., India) – 0.015, the highest – for Atoris (tab. coated a cover film 40 mg №90, KRKA, Slovenia) – 0.835; among drugs rosuvastatin the lowest for Rosart (tab. coated a cover film 5 mg №30, Actavis, Iceland) – 0.004, the highest – for Crestor (tab. cont. cover 20 mg №28, AstraZeneca, UK) – 1.660. Consequently, the most available drugs are: Zocor forte (tab. coated a cover 40 mg №14, Merck Sharp & Dohme Idea, Switzerland), Lovastatin (tab. 20 mg №30, Kievmedpreparat, Ukraine), Atormac (tab. coated a cover 20 mg №10, Macleods Pharmaceuticals Ltd., India), Rosart (tab. coated a cover film 5 mg №30, Actavis, Iceland), which in turn ensures high data flashy sales of drugs, because the relationship between price indicators and solvency of the drug the patient is a minor.

As to availability ratio, we can conclude that among drugs simvastatin the most affordable medication is Simvastat (tab. coated a cover film 10 mg №20, Hemofarm, Serbia) – 0.993; among drugs lovastatin it is Lovastatin (tab. 20 mg №30, Kievmedpreparat, Ukraine) – 0.985; among drugs atorvastatin – Atormac (tab. coated a cover 20 mg №10, Macleods Pharmaceuticals Ltd., India) – 0.995; among drugs rosuvastatin – Rosart (tab. coated a cover film 5 mg №30, Actavis, Iceland) – 0.987.

Sales policy analysis of statin drugs shows that domestic manufacturers for their drug choose two-level channel and intensive distribution. There is characteristically three-level channel and selective distribution for foreign drugs. Exclusive distribution is chosen for Merck Sharp & Dohme Idea, Switzerland (Zocor forte); IVAX Pharmaceuticals, Czech Republic (Simgal); Pfizer Inc., USA (Caduet); Ananta Medicare, Great Britain (Limistin); Nobel, Turkey (Tolevas); Lek, Slovenia (Tulip).

4.2 Pharmacoeconomical research

In the third part of the research, we compared the cost of course treatment for all study drugs by type of active ingredient. CCOHTA says there is no evidence of a difference in statin effectiveness [57]. Thus, these can be interchanged in clinical practice [58].

Using cost minimization analysis we conclude that among simvastatin drugs, the most economically feasible is Simvacard tab. coated a cover 40 mg blister №28, Zentiva (Czech Republic) – 89,21 ± 1,29 UAH; among atorvastatin drugs – ETSET® tab. coated a cover 40 mg blister №28, Kusum Pharm LLC (Ukraine) – 72,77 ± 8,00 UAH; among rosuvastatin drugs – Rosart tab. coated a cover film 40 mg №90, Actavis (Iceland) – 49,05 ± 26,63 UAH; among lovastatin drugs the rate for Lovastatin tab. 20 mg №30, Kievmedpreparat (Ukraine) is 172,19 ± 0,42 UAH.

A summary of the results of systematic reviews on the statin effect show a reduction in the risk of morbidity and mortality: mortality from all causes - 24 %, fatal myocardial infarction - 39 %, non-fatal myocardial infarction - 34 %, fatal stroke - 23 %, non-fatal stroke - 31 % [59]. Based on cost per package, each drug cost was calculated for 1 patient for 1 month of treatment and a cost of efficiency unit was established (cost-effectiveness ratio). Calculation of cost effectiveness ratios is shown in Table 2.

Table 2: Calculation using the cost-effectiveness analysis

N	*Name drugs, form release, manufacturer*	*Price, UAH*	*Cost for 1 patient for 1 month of treatment, UAH*	*Cost-effectiveness ratio*
Indicator reduce fatal myocardial infarction - 39%				
1.	Simvacard tab. coated a cover 40 mg blister №28, Zentiva (Czech Republic)	111,02	89,21	228,74
2.	Lovastatin tab. 20 mg №30, Kievmedpreparat (Ukraine)	76,53	172,19	441,51
3.	ETSET® tab. coated a cover 40 mg blister №28, Kusum Pharm LLC (Ukraine)	135,83	72,77	186,59
4.	Rosart tab. coated a cover film 40 mg №90, Actavis (Iceland)	588,58	49,05	125,77
Indicator reduce non-fatal myocardial infarction - 34%				
1.	Simvacard tab. coated a cover 40 mg blister №28, Zentiva (Czech Republic)	111,02	89,21	262,38
2.	Lovastatin tab. 20 mg №30, Kievmedpreparat (Ukraine)	76,53	172,19	506,44

3.	ETSET® tab. coated a cover 40 mg blister №28, Kusum Pharm LLC (Ukraine)	135,83	72,77	214,03
4.	Rosart tab. coated a cover film 40 mg №90, Actavis (Iceland)	588,58	49,05	144,26
Indicator reduce fatal stroke - 23%				
1.	Simvacard tab. coated a cover 40 mg blister №28, Zentiva (Czech Republic)	111,02	89,21	387,87
2.	Lovastatin tab. 20 mg №30, Kievmedpreparat (Ukraine)	76,53	172,19	748,65
3.	ETSET® tab. coated a cover 40 mg blister №28, Kusum Pharm LLC (Ukraine)	135,83	72,77	316,39
4.	Rosart tab. coated a cover film 40 mg №90, Actavis (Iceland)	588,58	49,05	213,26
Indicator reduce non-fatal stroke - 31%				
1.	Simvacard tab. coated a cover 40 mg blister №28, Zentiva (Czech Republic)	111,02	89,21	287,77
2.	Lovastatin tab. 20 mg №30, Kievmedpreparat (Ukraine)	76,53	172,19	555,45
3.	ETSET® tab. coated a cover 40 mg blister №28, Kusum Pharm LLC (Ukraine)	135,83	72,77	234,74
4.	Rosart tab. coated a cover film 40 mg №90, Actavis (Iceland)	588,58	49,05	158,23
Indicator decrease all-cause mortality - 24%				
1.	Simvacard tab. coated a cover 40 mg blister №28, Zentiva (Czech Republic)	111,02	89,21	371,71
2.	Lovastatin tab. 20 mg №30, Kievmedpreparat (Ukraine)	76,53	172,19	717,46
3.	ETSET® tab. coated a cover 40 mg blister №28, Kusum Pharm LLC (Ukraine)	135,83	72,77	303,21
4.	Rosart tab. coated a cover film 40 mg №90, Actavis (Iceland)	588,58	49,05	204,38

Calculated cost- effectiveness ratio results proved that the optimal choice is Rosart tab. coated a cover film 40 mg №90, Actavis (Iceland).

Meta-analysis showed that the most effective drugs for treatment of severe lipid metabolism disorders are synthetic statins: rosuvastatin 10 mg leads to an average 46% low-density lipoprotein reduction, atorvastatin 10 mg – 37 %, simvastatin 40 mg – 39%, pravastatin 40 mg – 30 % [36], lovastatin 45 mg – 31 %, fluvastatin 60 mg – 33% [32].
Calculations computing are presented in Table 3.

Table 3: Calculation using the cost-utility analysis

N	*Name drugs, form release, manufacturer*	*Price, UAH*	*Cost for 1 patient for 1 month of treatment, UAH*	*Cost-utility ratio*
1.	Simvacard tab. coated a cover 40 mg blister №28, Zentiva (Czech Republic)	111,02	118,95	305,00
2.	Lovastatin tab. 20 mg №30, Kievmedpreparat (Ukraine)	76,53	172,19	555,45
3.	ETSET® tab. coated a cover 40mg blister №28, Kusum Pharm LLC (Ukraine)	135,83	36,38	98,32
4.	Rosart tab. coated a cover film 40 mg №90, Actavis (Iceland)	588,58	49,05	106,63

According to the results of the calculations, ETSET® tab. coated a cover 40 mg blister №28, Kusum Pharm LLC (Ukraine) provides the reduction of low-density lipoprotein at lower cost.

4.3 Recommendations by State Formulary of Drugs in Ukraine

The State Formulary of Drugs in Ukraine assigned statin drugs to group 2. Cardiology. Medicines. 2.16. Lipid-lowering drugs. 2.16.1. Reductase inhibitors 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) or statins. The range of statins registered in the Formulary, include data on Atorvastatin, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin and Fluvastatin. The State Formulary of Drugs in Ukraine contains information on the pharmacotherapeutic action, selection, prescribing, destination features, and rules for dispensing drugs. Since 2013, the defined daily dose (DDD) and DDD price have been listed for most statins. When conducting a comparative assessment issued by seven Issues of State Formulary of Drugs in Ukraine (2009-2015 years) [60-66] we found differences in all drug groups.
All Issues of the Formulary contain drugs based on Atorvastatin per 10 mg, 20 mg, 40 mg and 80 mg. Defined daily dose: orally - 20 mg. Every year there are different trade names. First Issue recommended to select 30 trade names atorvastatin [60], Second Issue - 29 [61], Third Issue - 33 [62], Fourth Issue - 29 [63], Fifth Issue - 95 [64], Sixth Issue - 74 [65], Seventh Issue - 58 [66]. For drugs of first choice include only domestic medicines of Atorvastatin: Atorvacor® "Farmak" JSC, Atorvastatin "Lvivthechnopharm" LLC, Livostor "Kiev vitamin factory" JSC, Lipicard "Chervona Zirka" CPP [60]; Atorvacor® "Farmak" JSC, Atorvastatin "Lvivthechnopharm" LLC, Atorvastatin Tekhnomed "Tekhnomed" LLC, Livostor "Kiev vitamin factory" JSC, Lipiks "Chervona Zirka" CPP [61]; Atorvacor® "Farmak" JSC, Vazoklyn "Pharmaceutical firm "Darnytsia", Etset® "Kusum Healthcare Pvt." LTD/"Kusum Pharm" LLC, Livostor "Kiev vitamin factory" JSC, Lipiks "Chervona Zirka" CPP, Atorvastatin Tekhnomed 20 mg "Tekhnomed" LLC [62]; Atorvacor® "Farmak" JSC, Atorvastatin Tekhnomed "Tekhnomed" LLC, Vazoklyn "Pharmaceutical firm "Darnytsia", Etset® "Kusum Healthcare Pvt." LTD/"Kusum Pharm" LLC, Livostor "Kiev vitamin factory" JSC, Lipiks "Chervona Zirka" CPP [63]; Atorvacor® "Farmak" JSC, Atorvastatin Tekhnomed 20 mg "Tekhnomed" LLC, Vazoklyn "Pharmaceutical firm "Darnytsia", Etset® "Kusum Healthcare Pvt." LTD/"Kusum Pharm" LLC, Livostor "Kiev vitamin factory" JSC, Lipiks "Chervona Zirka" CPP [64]; Atorvacor® "Farmak" JSC, Atorvastatin Tekhnomed 20 mg "Tekhnomed" LLC, Vazoklyn "Pharmaceutical firm "Darnytsia", Etset® "Kusum Healthcare Pvt." LTD/"Kusum Pharm" LLC, Livostor "Kiev vitamin factory" JSC [65]; Atorvacor® "Farmak" JSC, Vazoklyn "Pharmaceutical firm "Darnytsia", Etset® "Kusum Healthcare Pvt." LTD/"Kusum Pharm" LLC, Livostor "Kiev vitamin factory" JSC [66].

Group Lovastatin is less numerous. Defined daily dose: orally - 45 mg. It should be noted that the first three Issues of State Formulary of Drugs in Ukraine included this group per 10 mg, 20 mg and 40 mg. From 2012, the Formulary proposed lovastatin tablets of 20 mg. First Issue recommends

Lovacor "Kievmedpreparat", Lovastatin "Kievmedpreparat", Liproks "Biofarm Ltd" (Poland), LovaHexal® "Salutas Pharma GmbH" venture company "Hexal AG" (Germany), Lovastatin "Biofarm Ltd" (Poland), Mevakor "Merck Sharp & Dohme BV" of Corporation "Merck Sharp & Dohme" (Netherlands/USA) [60], Second Issue - Lovakor "Kievmedpreparat", Lovastatin "Kievmedpreparat", Liproks "Biofarm Ltd" (Poland), LovaHexal® "Salutas Pharma GmbH" venture company "Hexal AG" (Germany), Lovastatin "Biofarm Ltd"(Poland), Mevakor "Merck Sharp & Dohme BV" of Corporation "Merck Sharp & Dohme" (Netherlands/USA) [61], Third Issue - only Lovastatin "Kievmedpreparat" and LovaHexal® "Salyutas Pharma GmbH" venture company "Hexal AG" (Germany) [62], another Issues - only Lovastatin "Kievmedpreparat" [63-66].
From the group of drugs Pravastatin, First Issue recommended tablets 10 mg, 20 mg with trade name Lipostat "Bristol-Myers Squibb" (France), Pravastatin Sandoz "Sandoz Pharmaceuticals d.d." (Slovenia) [60]. Second Issue offered similar drugs in doses 10 mg, 20 mg, 40 mg [61]. The next three Issues focused on Pravastatin Sandoz tablets 10 mg, 20 mg, 40 mg "Pharmaceutical company "Lek DD" venture company "Sandoz" (Slovenia) [62-64]. Sixth and Seventh Issues recommended Pravapres® tablets 20 mg "Unifarm" JSC (manufacture product in balk, primary and secondary packaging) / "Sofarma" JSC (authorization to issue series) (Bulgaria) [65,66].

Among drugs Rosuvastatin, all Issues of the Formulary recommended to use coated tablets 10 mg, 20 mg, 40 mg. Defined daily dose: orally - 10 mg. But unity of choice of trade names was not found. Thus, the first three editions offered Krestor "IPR Pharmaceuticals Inc." (Puerto Rico/US) [60-62]. This option, Mertenil "Gedeon Richter"/"Gedeon Richter-Rus" JSC (Hungary/Russian Federation) and Rozart "Actavis Ltd" (Malta) was added in 2012 [63]. Fifth Issue contains 28 drugs rosuvastatin for these trade names: Krestor "IPR Pharmaceuticals Inc." (Puerto Rico/US), Mertenil "Gedeon Richter"/"Gedeon Richter-Rus" JSC (Hungary/Russian Federation), Rozart "Actavis Ltd" (Malta), Rozukard® "Zentiva" Ltd (Czech Republic), Rozulip "Pharmaceutical factory "Egis" JSC (Hungary), Roxera "KRKA" DD (Slovenia) [64]. Since 2014, the State Formulary of Drugs in Ukraine replenished domestic drug Klivas "Pharma Start" LLC and Rosuvastatin Sandoz® "Pharmaceutical company "Lek" DD (Slovenia) [65]. Seventh Issue contains additional Roviks "Apotex Inc." (Canada), Rozvator "Ranbaxi Laboratories Limited" (India), Romazyk Pharmaceutical Works "Polpharma" S.A. (Poland), Fastron "Actavis" Ltd (Malta) and has 39 drugs [66].

The State Formulary encourages simvastatin in coated tablets 10 mg, 20 mg, 40 mg. Defined daily dose: orally - 30 mg. Group Simvastatin is quite numerous. First and Second Issues include 29 trade names [60,61], Third Issue - only 16 [62], Fourth Issue - 19 [63], Fifth Issue - already 50 [64], Sixth Issue - 35 [65], Seventh Issue - 29 [66]. Fatherland drugs of simvastatin are: Vazostat Zdorovya "Pharmaceutical company "Zdorovya" LLC, Simvacor®-Darnitsa "Pharmaceutical firm "Darnytsia" JSC [60-66], only in 2012-2014 it has added Simvostat "Pharmex Group" LLC [63-65].
For drugs simvastatin there are also recommended by the Formulary: Allesta® "Alkaloid Skopje" (the Republic of Macedonia), Vabadyn® "Atlantic Pharma - Produces Pharmaceuticals" S.A. (production in bulk) / "Menarini-Von Heyden" GmbH (final packaging control and batch release) (Portugal/Germany), Vasilip® "KRKA" DD (Slovenia), Vasta "Tabuk Pharmaceutical Manufacturing Co." (Saudi Arabia), Zocor® "Merck Sharp & Dohme BV " (Packing, batch release) / "Merck Sharp & Dohme Limited" (manufacturer production in balk, quality control) (Netherlands/UK), Zosta "Usv Limited" (India), Cardak "Aurobindo Pharma Limited" (India), Simvacard "Zentiva" LLC (Czech Republic), Simvatin® "Pharma International" (Jordan), Simgal "Teva Czech Industries s.r.o." (Czech Republic), Simstat "Lupin Limited" (India) [66].

For Fluvastatin, defined daily dose: orally - 60 mg. The only representative of Fluvastatin was 80 mg coated tablet with trade name Lescol®XL "Novartis Pharmaceutica S.A." (Spain) [60-66].

4.4 Discussion

In this work, we reviewed general and detailed recommendations on the choice of statin drugs.

Our results showed that despite the large evidence base studies, the effects of statins were confirmed in the primary and secondary prevention of cardiovascular disease. However, the studied group of drugs are not widely used in practice. Thus, the drugs pravastatin and fluvastatin are registered in Ukraine, but are missing on the market. We do not have drug pivastatin.

The research provides a few medications that are most appropriate to apply in our practice. As we know, the in choosing a drug the doctor must take into account such factors as high efficiency, safety and profitability of long-term therapy. We determined a drug that fits the bill. It is a drug based on rosuvastatin. Our results of intense study showed clinical efficacy and safety advantages. Admittedly, rosuvastatin is characterized from other statins by its pharmacological properties, high lipid-lowering activity and clinical efficacy, especially in patients at high risk of cardiovascular complications. The evidence suggests that rosuvastatin has the most potent effects on the lowering of low-density lipoprotein, high-density lipoprotein, triglyceride and C-reactive protein. Ongoing outcomes studies will determine whether the beneficial effects of rosuvastatin translate into reduced morbidity and mortality. Based on the identified literature, there is no significant difference in the rates of adverse events between rosuvastatin and other statins. In recent years, we also see significant expansion of recomendations to prescribe rosuvastatin by The State Formulary of Drugs in Ukraine, although rosuvastatin drugs make up only 16% of the market. Presently, branded and generic simvastatin, are produced and supplied by domestic and foreign firms. Statin drugs are not cheap, and some are very expensive. Rosart tab. coated a cover film 40 mg №90, Actavis (Iceland) received pharmacoeconomic benefit in Ukraine. In patients with hypercholesterolemia in British Columbia, rosuvastatin 10 mg was more cost-effective than

the most frequently used doses of atorvastatin (10 and 20 mg), generic simvastatin (20 and 40 mg) and generic pravastatin (20 and 40 mg) [67]. Rosuvastatin may represent an attractive choice compared with likely alternative existing therapies used in the primary and secondary prevention of cardiovascular events by the National Health Service of Greece [68].

We also received clinical data for atorvastatin. Atorvastatin is more than three-fold less potent than rosuvastatin, the cholesterol-lowering effects of atorvastatin are greater in females than in males and greater in non-familial than in familial hypercholesterolaemia. In Ukraine drugs based on atorvastatin occupy more than half the market share of statins. The swing of prices for drugs in this group is quite substantial. Among the drugs atorvastatin shall prevail ETSET® tab. coated a cover of 40 mg blister №28, Kusum Pharm LLC (Ukraine), that provides reducing of low-density lipoprotein at lower cost. State Formulary of Medicines in Ukraine also recommends it as one of the options.

Drugs based on simvastatin are long and have frequent practical application, the most reliable results at the clinical efficacy of cardio vascular diseases, are safe. Simvastatin is significantly more effective than all statins in lowering triglyceride and remnant lipoprotein cholesterol. In Ukraine there is a significant amount of drugs simvastatin (31% of statin). Prices for drugs simvastatin are set appropriately and fluctuate within 20% difference between the suppliers. Given the cost of treatment, it is advisable to appoint Simvacard tab. coated a cover of 40 mg blister №28, Zentiva (Czech Republic).

We also examined the market share of lovastatin, which is only 2%. The most affordable medication is Lovastatin tab. 20 mg №30, Kievmedpreparat (Ukraine). It is also recommended by State Formulary of Drugs in Ukraine.

5. Conclusions

When studying the pharmaceutical market of statins it was found that the largest number of patients take drugs based on atorvastatin (51%), drugs simvastatin occupy 31% rosuvastatin - 16%, lovastatin - 2%. The share of domestic lipid-lowering drugs is 17%. Among producers, undisputed leaders are Darnitsya, Farmex and Kusum Pharm Group, each holding 25%.

On the basis of evidence-based medicine it was conducted generalization of research results statin drugs.

By the cost minimization analysis it was calculated that the least costly are Simvacard tab. coated a cover 40mg blister №28, Zentiva (Czech Republic); Lovastatin tab. 20mg №30, Kievmedpreparat (Ukraine); ETSET® tab. coated a cover 40 mg blister №28, Kusum Pharm LLC (Ukraine); Rosart tab. coated a cover film 40mg №90, Actavis (Iceland). By pharmacoeconomic studies the cost-effectiveness analysis it was confirmed the lowest cost per unit of effectiveness for Rosart tab. coated a cover film 40mg №90, Actavis (Iceland). The cost-utility analysis proved that the best meets the needs of consumers ETSET® tab. coated a cover 40 mg blister №28, Kusum Pharm LLC (Ukraine).

When conducting comparative assessment issued by seven Issues of State Formulary of Drugs in Ukraine (2009-2015 years) we found differences filling of the group drugs. It was well-founded pharmacoeconomic benefit rosuvastatin 10 mg for reducing the risk of morbidity and mortality, atorvasatin 10 mg for reducing of low-density lipoprotein.

6. Future Scope

The proposed algorithm research would be methodical to choice a rational treatment.

References

[1] Health profile: Ukraine. World Health Rankings. http://www.worldlifeexpectancy.com/country-health-profile/ukraine/ ; 2014 Accessed 18.03.16.
[2] Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. Lancet. 2014;384:626-635 http://dx.doi.org/10.1016/S0140-6736(14)61177-6
[3] Varbo A, Benn M, Tybjærg-Hansen A, Jørgensen AB, Frikke-Schmidt R, Nordestgaard BG. Remnant cholesterol as a causal risk factor for ischemic heart disease. Journal of the American College of Cardiology. 2013;61:427-36. doi: 10.1016/j.jacc.2012.08.1026.
[4] David C. Goff Jr, Donald M. Lloyd-Jones, Sean Coady et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129 [suppl 2]:S49-S73 doi:10.1161/01.cir.0000437741.48606.98 http://circ.ahajournals.org/content/129/25_suppl_2/S49.full
[5] Terry A. Jacobson, Matthew K. Ito, Kevin C. Maki et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1 – executive summary. Journal Clinical Lipidology. 2014;8(5):473-488. http://dx.doi.org/10.1016/j.jacl.2014.07.007 http://www.lipidjournal.com/article/S1933-2874(14)00274-8/fulltext
[6] Rishi K. Wadhera, Dylan L. Steen, Irfan Khan, Robert P. Giugliano, JoAnne M. Foody. A review of low-density lipoprotein cholesterol, treatment strategies, and its impact on cardiovascular disease morbidity and mortality. Journal Clinical Lipidology. 2015:1-18 http://dx.doi.org/10.1016/j.jacl.2015.11.010
[7] David Newman. Statin Drugs Given for 5 Years for Heart Disease Prevention (Without Known Heart Disease). The NNT. http://www.thennt.com/nnt/statins-for-heart-disease-prevention-without-prior-heart-disease/ ; 2015 Accessed 19.03.16.
[8] Miller M, Stone NJ, Ballantyne C et al. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2011;123:2292-2333 doi: 10.1161/CIR.0b013e3182160726 http://circ.ahajournals.org/content/123/20/2292.full

[9] Infiniti Research Limited. Global Statin Market 2015-2019. Tenbury: Report Buyer Ltd; 2015. https://www.reportbuyer.com/product/3095480/global-statin-market-2015-2019.html/
[10] Rachel Cooper. Statins: the drug firms' goldmine. The Telegraph. www.telegraph.co.uk/news/health/news/8267876/Statins-the-drug-firms-goldmine.html/ ; 2011 Accessed 19.03.16.
[11] Terry A. Jacobson, Kevin C. Maki, Carl E. Orringer et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 2. Journal Clinical Lipidology. 2015;9,6:S1-S122. http://dx.doi.org/10.1016/j.jacl.2015.09.002 http://www.lipidjournal.com/article/S1933-2874(15)00380-3/fulltext
[12] Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:2889-2934. doi: 10.1016/j.jacc.2013.11.002. Epub 2013 Nov 12.
[13] Sudhir K. Unni, Ruben G.W. Quek, Joseph Biskupiak, Vinson C. Lee, Xiangyang Ye, Shravanthi R. Gandra. Assessment of statin therapy, LDL-C levels, and cardiovascular events among high-risk patients in the United States. Journal Clinical Lipidology. 2016;10,1:63-71. http://dx.doi.org/10.1016/j.jacl.2015.09.008 http://www.lipidjournal.com/article/S1933-2874(15)00386-4/fulltext
[14] Blankenhorn DH, Azen SP, Kramsch DM et al. Coronary angiographic changes with lovastatin therapy. The Monitored Atherosclerosis Regression Study. Ann Intern Med. 1993;119:969-976
[15] Waters D. Higginson L, Gladstone P. et al. Effects of monotherapy with an HMG-CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography. The Canadian Coronary Atherosclerosis Intervention Trial. Circulation. 1994;344:633-638.
[16] MAAS Investigators. Effect of simvastatin on coronary atheroma: the Multicentre Anti-atheroma Study (MAAS). Lancet. 1994;344:633-638.
[17] Pitt B, Mancini GBJ, Ellis SG et al. Pravastatin Limitation of Atherosclerosis in the Coronary arteries (PLAC-1): reduction in atherosclerosis progression and clinical events. J Am Coll Cardiol. 1995;26:1133-1139.
[18] Scandinavian Simvastatin Survival Study Group. Randomised trial ofcholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344:1383-1389.
[19] Sacks FM, Pfeffer MA, Moye LA et al, for the Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med. 1996;335:1001-1009.
[20] Long-term Intervention with Pravastatin inIschaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med. 1998;339:1349-1357.
[21] Shepard J, Cobb SM, Ford I et al, for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med. 1995;333:1301-1307.
[22] Downs JR, Clearfield M, Weis S et al, for the AFCAPS /TexCAPS Research Group. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS /TexCAPS. JAMA. 1998;279:1615-1622.
[23] Prevention of Coronary Heart Disease in Clinical Practice. Recommendations of the Second Joint Task Force of the European and other Societies on Coronary Prevention. Eur Heart J. 1998;19:1434-1503.
[24] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA. 2001;285:2486-2497.
[25] Dyslipidemias: Pathophysiology, Evaluation and Management. Editors: Abhimanyu Garg. Humana Press; 2015. DOI 10.1007/978-1-60761-424-1
[26] Vale N, Nordmann AJ, Schwartz GG, de Lemos J, Colivicchi F, den Hartog F, Ostadal P, Macin SM, Liem AH, Mills EJ, Bhatnagar N, Bucher HC, Briel M. Statins for acute coronary syndrome. Cochrane Database of Systematic Reviews. 2014;9:CD006870. DOI: 10.1002/14651858.CD006870.pub3. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006870.pub3/epdf
[27] Taylor F, Huffman MD, Macedo AF, Moore THM, Burke M, Davey Smith G, Ward K, Ebrahim S. Statins for the primary prevention of cardiovascular disease (Rewiev). Cochrane Database of Systematic Reviews. 2013;1:CD004816. DOI: 10.1002/14651858.CD004816.pub5 http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004816.pub5/epdf
[28] Smith MEB, Lee NJ, Haney E, Carson S. Drug Class Review: HMG-CoA Reductase Inhibitors (Statins) and Fixed-dose Combination Products Containing a Statin: Final Report Update 5. Drug Class Reviews. Portland (OR): Oregon Health & Science University; 2009. http://www.ncbi.nlm.nih.gov/books/NBK47273/
[29] Manktelow BN, Potter JF. Interventions in the management of serum lipids for preventing stroke recurrence (Rewiev). Cochrane Database of Systematic Reviews. 2009;3:CD002091. DOI: 10.1002/14651858.CD002091.pub2 http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002091.pub2/epdf
[30] Adams SP, Tsang M, Wright JM. Lipid-lowering efficacy of atorvastatin. Cochrane Database Syst Rev. 2015;3:CD008226. doi: 10.1002/14651858.CD008226.pub3.

[31] Schaefer EJ, McNamara JR, Tayler T, Daly JA, Gleason JL, Seman LJ, Ferrari A, Rubenstein JJ. Comparisons of effects of statins (atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin) on fasting and postprandial lipoproteins in patients with coronary heart disease versus control subjects. Am J Cardiol. 2004;93(1):31-39. DOI: http://dx.doi.org/10.1016/j.amjcard.2003.09.008

[32] David Waters, Gregory G Schwartz, Anders G Olsson. The Myocardial Ischemia Reduction with Acute Cholesterol Lowering (MIRACL) trial: a new frontier for statins? Curr Control Trials Cardiovasc Med. 2001;2(3):111-114. doi: 10.1186/cvm-2-3-111 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC59635/

[33] Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, Zeiher A, Chaitman BR, Leslie S, Stern T; Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA. 2001;285(13):1711-1718. doi:10.1001/jama.285.13.1711. http://jama.jamanetwork.com/article.aspx?articleid=193709

[34] Schuster H. The GALAXY Program: an update on studies investigating efficacy and tolerability of rosuvastatin for reducing cardiovascular risk. Expert Rev Cardiovasc Ther. 2007;5(2):177-193. DOI:10.1586/14779072.5.2.177 http://www.tandfonline.com/doi/pdf/10.1586/14779072.5.2.177?redirect=1

[35] Canadian Agency for Drugs and Technologies in Health. Comparative Effectiveness of Rosuvastatin Versus Other Statins: A Review of Clinical Effectiveness. CADTH Rapid Response Service. 2011:21 https://www.cadth.ca/media/pdf/htis/feb-2011/L0247-Rosuvastatin_final.pdf

[36] Jones PH, Davidson MH, Stein EA et al. Comparison of the Efficacy and Safety of Rosuvastatin Versus Atorvastatin, Simvastatin and Pravastatin Across Doses (STELLAR Trial). Am J Cardiol. 2003;92:152-60.

[37] Jones PH, Hunninghake DB, Ferdinand KC, Stein EA, Gold A, Caplan RJ, Blasetto JW; Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin Study Group.Effects of rosuvastatin versus atorvastatin, simvastatin, and pravastatin on non-high-density lipoprotein cholesterol, apolipoproteins, and lipid ratios in patients with hypercholesterolemia: additional results from the STELLAR trial. Clin Ther. 2004;26(9):1388-1399. http://www.ncbi.nlm.nih.gov/pubmed/15531001

[38] Adams SP, Sekhon SS, Wright JM. Lipid-lowering efficacy of rosuvastatin. Cochrane Database Syst Rev. 2014;11:CD010254. doi: 10.1002/14651858.CD010254.pub2.

[39] Crouse JR 3rd, Raichlen JS, Riley WA, Evans GW, Palmer MK, O'Leary DH, Grobbee DE, Bots ML. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. JAMA. 2007;297(12):1344-53. http://www.ncbi.nlm.nih.gov/pubmed/17384434

[40] Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359(21):2195-207. doi:10.1056/NEJMoa0807646 http://www.nejm.org/doi/pdf/10.1056/NEJMoa0807646

[41] Ballantyne CM, Bertolami M, Hernandez Garcia HR, Nul D, Stein EA, Theroux P, Weiss R, Cain VA, Raichlen JS. Achieving LDL cholesterol, non-HDL cholesterol, and apolipoprotein B target levels in high-risk patients: Measuring Effective Reductions in Cholesterol Using Rosuvastatin therapY (MERCURY) II. Am Heart J. 2006;151(5):975.e1-9. DOI: http://dx.doi.org/10.1016/j.ahj.2005.12.013 http://www.ahjonline.com/article/S0002-8703(06)00016-0/fulltext

[42] Schuster H, Barter PJ, Stender S, Cheung RC, Bonnet J, Morrell JM, Watkins C, Kallend D, Raza A. Effects of switching statins on achievement of lipid goals: Measuring Effective Reductions in Cholesterol Using Rosuvastatin Therapy (MERCURY I) study. Am Heart J. 2004;147(4):705-712. DOI: http://dx.doi.org/10.1016/j.ahj.2003.10.004 http://www.ahjonline.com/article/S0002-8703(03)00710-5/fulltext

[43] Scott M. Grundy (Chair of the panel) et al. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Circulation. 2002;106:3143-3421. http://www.nhlbi.nih.gov/sites/www.nhlbi.nih.gov/files/Circulation-2002-ATP-III-Final-Report-PDF-3143.pdf

[44] Third Report of the National Cholesterol Education Program (NCEP). Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Executive Summary. http://www.nhlbi.nih.gov/files/docs/guidelines/atp3xsum.pdf/ ; 2001 Accessed 23.03.2016

[45] Byington RP, Davis BR, Plehn JF, White HD, Baker J, Cobbe SM, Shepherd J. Reduction of stroke events with pravastatin: the Prospective Pravastatin Pooling (PPP) Project. Circulation. 2001;103(3):387-392. http://circ.ahajournals.org/content/103/3/387.full

[46] Chapman MJ. Pitavastatin: novel effects on lipid parameters. Atheroscler Suppl. 2011;12(3):277-84. doi: 10.1016/S1567-5688(11)70887-X.

[47] Tamio Teramoto. Pitavastatin: Clinical effects from the LIVES Study. Atheroscler Suppl. 2011;12(3):285-288. DOI: http://dx.doi.org/10.1016/S1567-5688(11)70888-1

[48] Beatrice A. Golomb, Joel E. Dimsdale, Hayley J. Koslik, Marcella A. Evans, Xun Lu, Steven Rossi, Paul J. Mills, Halbert L. White, Michael H. Criqui. Statin Effects on Aggression: Results from the UCSD Statin Study, a Randomized Control Trial. PLOS One. http://dx.doi.org/10.1371/journal.pone.0124451/ ; 2015 Accessed 01.04.16.

[49] Bhavan Kumar et al. A review on risks involved in statin therapy. Int J Pharm. 2015;5(1):248-252. http://pharmascholars.com/pharma/upload/pharmacy_552e5560421a4.pdf?title=A%20REVIEW%20ON%20RIS

KS%20INVOLVED%20IN%20STATIN%20THERAPY
[50] Ministry of Health of Ukraine. State Register of Medicines Ukraine. http://www.drlz.com.ua/ ; 2016 Accessed 16.03.16.
[51] Trygubchak O.V., Voytkova L.S. Trend Analysis of Combined Drugs Creation (for example Acetylsalicylic Acid). Journal of Pharmacy and Pharmacology. 2015:10(3):451-462. doi: 10.17265/2328-2150/2015.10.002
[52] Weekly Pharmacy Online. The Price of Medicines: Wholesale and Retail Offers. http://pharmbase.com.ua / ; 2016 Accessed 24.02.16, 19.03.16.
[53] Tanner John F. (Jeff), Raymond Mary Anne. Marketing Principles (v. 1.0). Creative Commons; 2012. http://2012books.lardbucket.org/pdfs/marketing-principles-v1.0.pdf
[54] Wiley Online Library. EBM Guidelines: Evidence-Based Medicine. www.onlinelibrary.wiley.com/book/10.1002/0470057203/ ; 2016 Accessed 21.03.16 DOI: 10.1002 / 0470057203
[55] Renee J. G. Arnold. Pharmacoeconomics: From Theory to Practice. Boca Raton, London, New York: CRC Press, Taylor and Francis Group; 2010.
[56] State enterprise "State Expert Center of the Ministry of Health of Ukraine". Information retrieval system "Electronic Form". http://www.dec.gov.ua/index.php/ua/informatsijno-poshukova-sistema-elektronnij-formulyar/ ; 2016. Accessed 31.03.16
[57] No evidence of a difference in statin effectiveness, says CCOHTA. Inpharma Weekly. 1998;1142(1):6. DOI 10.2165/00128413-199811420-00010
[58] Nur Jaharat Lubna, et al. Comparative in vitro pharmaceutical equivalence studies of different brands of atorvastatin calcium tablets marketed in Bangladesh. Int J Pharm. 2015;5(2):347-351. http://pharmascholars.com/pharma/upload/pharmacy_552e5d8dccce7.pdf?title=COMPARATIVE%20IN%20VITRO%20PHARMACEUTICAL%20EQUIVALENCE%20STUDIES%20OF%20DIFFERENT%20BRANDS%20OF%20ATORVASTATIN%20CALCIUM%20TABLETS%20MARKETED%20IN%20BANGLADESH
[59] Initiating statin therapy at hospital discharge associated with reduced mortality Inpharma Weekly. 2001;1275(1):14. DOI 10.2165/00128413-200112750-00033
[60] Chumak VT, Mal'cev VI, Morozov AM, Parij VD, Stepanenko AV. State Formulary of Drugs. First Issue. Kiev: SE State Pharmacological Center MHC Ukraine; 2009.
[61] Chumak VT, Mal'cev VI, Morozov AM, Parij VD, Stepanenko AV. State Formulary of Drugs. Second Issue. Kiev: SE State Pharmacological Center MHC Ukraine; 2010.
[62] Blihar VJe, Chumak VT, Mal'cev VI, Morozov AM, Parij VD, Stepanenko AV, Dumenko TM. State Formulary of Drugs. Third Issue. Kiev: SE State Pharmacological Center MHC Ukraine; 2011.
[63] Blihar VJe, Mal'cev VI, Morozov AM, Parij VD, Stepanenko AV, Dumenko TM. State Formulary of Drugs. Fourth Issue. Kiev: SE State Pharmacological Center MHC Ukraine; 2012.
[64] Annex to the Order of Ministry of Health of Ukraine №251, 29.03.2013. State Formulary of Drugs. Fifth Issue. Kiev: SE State Pharmacological Center MHC Ukraine; 2013.
[65] Annex to the Order of Ministry of Health of Ukraine № 252, 08.04.2014. State Formulary of Drugs. Sixth Issue. Kiev: SE State Pharmacological Center MHC Ukraine; 2014.
[66] Annex to the Order of Ministry of Health of Ukraine № 183, 31.03.2015. State Formulary of Drugs. Seventh Issue. Kiev: SE State Pharmacological Center MHC Ukraine; 2015.
[67] Costa-Scharplatz M, Ramanathan K, Frial T, Beamer B, Gandhi S. Cost-effectiveness analysis of rosuvastatin versus atorvastatin, simvastatin, and pravastatin from a Canadian health system perspective. Clin Ther. 2008;30(7):1345-1357. http://www.ncbi.nlm.nih.gov/pubmed/18691996
[68] Fragoulakis V, Kourlaba G, Maniadakis N. Economic evaluation of statins in high-risk patients treated for primary and secondary prevention of cardiovascular disease in Greece. Clinicoecon Outcomes Res. 2012;4:135-43. doi: 10.2147/CEOR.S31376. http://www.ncbi.nlm.nih.gov/pubmed/22719213.

Author Profile

Oksana Tryhubchak studed at Ternopil State Medical University by I.Ya. Horbachevsky specialty pharmacy in 2000-2005, graduated with honors. She received the PhD in Pharmaceutical Sciences from Danylo Halytsky Lviv State Medical University in 2010. During 2006-2011, she was pharmacist in central pharmacy in Ternopil. From 2006 till 2016 she have worked as assistant professor of Department of management and economics of pharmacy with technology drugs in Ternopil State Madical University by I.Ya. Horbachevsky. In 2013 got scientific rate associate professor. Now she is staying in Technical laboratory R&D department of pharmaceutical manufacture JSC Farmak.