Ф А 2.2.1-32-367

MINISTRY OF HEALTH OF UKRAINE
NATIONAL UNIVERSITY OF PHARMACY
pharmaceutical faculty
department of pharmacology and clinical pharmacy

QUALIFICATION WORK

on the topic: «**EVALUATION OF MEDICATION ADHERENCE AMONG CHRONIC CORONARY HEART DISEASE MOROCCAN PATIENTS USING COMBINATION THERAPY WITH ROSUVASTATIN**»

Prepared by: higher education graduate of group
(Фм20(4,10д) англ-04)
specialty 226 Pharmacy, industrial pharmacy
educational and professional program Pharmacy
Omar ELKADIRI
Supervisor: associate professor of higher education institution
of department of pharmacology and clinical pharmacy, PhD,
associate professor Inna OTRISHKO
Reviewer: head of the department of clinical pharmacology
of the Institute for Advanced Training of Pharmacy Specialists
of the National University of Pharmacy, DSc,
professor Yaroslava BUTKO

Kharkiv – 2025

ANNOTATION

Omar ELKADIRI. Evaluation of medication adherence among chronic coronary heart disease Moroccan patients using combination therapy with rosuvastatin. – The manuscript. – National University of Pharmacy of Ministry of Healthcare of Ukraine, Kharkiv, 2025.

The qualification work is devoted to the study of the Evaluation of medication adherence among chronic coronary heart disease Moroccan patients using combination therapy with rosuvastatin.

Qualification work is presented on 40 pages of typewritten text, consists of summary, introduction, 3 chapters, conclusions, references. The work is illustrated with 10 tables, 5 figures. The list of references contains 31 resources.

Key words: chronic coronary heart disease, rosuvastatin, efficacy and safety of therapy, medication adherence, Moroccan patients

АНОТАЦІЯ

Омар ЕЛЬКАДІРІ. Оцінка рівня прихильності до лікування марокканських пацієнтів з хронічною ішемічною хворобою серця при застосуванні препаратів розувастатину у складі комбінованої терапії. – На правах рукопису. – Національний фармацевтичний університет МОЗ України, Харків, 2025.

Кваліфікаційна робота присвячена вивченню рівня прихильності до лікування марокканських пацієнтів з хронічною ішемічною хворобою серця при застосуванні препаратів розувастатину у складі комбінованої терапії.

Кваліфікаційна робота викладена на 40 сторінках машинописного тексту, складається з резюме, вступу, 3 розділів, висновків, списку літератури. Робота проілюстрована 10 таблицями, 5 рисунками. Список літератури містить 31 найменування.

Ключові слова: хронічна ішемічна хвороба серця, розувастатин, ефективність та безпека терапії, прихильність до лікування, пацієнти із Марокко

CONTENT

INTRODUCTION

Relevance of the topic. Coronary heart disease (CHD) occurs as a result of absolute or relative impairment of myocardial blood supply due to coronary artery demage. A constant lack of blood supply to a particular area of the heart causes the development of chronic CHD, which can lead to sudden arrhythmia, coronary artery occlusion, myocardial infarction (MI), and even death. Therefore, diagnosis, adequate treatment and proper care of such patients are very important. The American Heart Association (AHA, 2023) and the American College of Cardiology (ACC, 2023), in collaboration with leading medical communities, have developed guidelines for the management of patients with chronic coronary artery disease that combine existing recommendations and the latest scientific evidence [1].

The ultimate goals of treating patients with chronic coronary heart disease are to prolong survival and improve quality of life. For this purpose, therapy should be aimed at reducing the incidence of cardiac death, non-fatal ischemic events, slowing the progression of atherosclerosis, as well as symptoms and functional limitations of chronic CHD, taking into account the patient's wishes, potential complications of procedures/drugs, and costs to the healthcare system [2].

Statins are among the most frequently prescribed drugs in highly developed countries. The high demand for this class of drugs is due to their proven high efficacy in the treatment of lipid metabolism disorders, prevention and treatment of coronary diseases caused by atherosclerotic vascular lesions. Statins are prescribed to patients with cardiovascular diseases of atherosclerotic origin (myocardial infarction, stable and unstable angina, atherosclerotic coronary lesions detected by angiography, coronary or any other arterial revascularization surgery, stroke, transient ischemic attack, documented carotid artery disease, lower extremity atherosclerosis, abdominal aortic aneurysm), patients with diabetes mellitus, chronic kidney disease to prevent cardiovascular complications, and patients with dyslipidemia or familial hypercholesterolemia.

Statins, which competitively inhibit the key enzyme of cholesterol synthesis,

3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, have revolutionized the prevention of cardiovascular disease (CVD). Due to their high lipid-lowering power and a range of pleiotropic properties, statins prevent the development of cardiovascular events [3].

Different statins have different potencies. For example, rosuvastatin is more potent than atorvastatin, simvastatin, lovastatin, pravastatin, and fluvastatin. Statins are classified into three generations based on their ability to lower low-density lipoprotein cholesterol (LDL-C) and into two groups based on their physicochemical properties. The first generation of statins entered the pharmaceutical market in the late 1980s and early 1990s. This generation is characterized by the lowest potency. The second generation – simvastatin and atorvastatin – had a higher potency, providing a 30% reduction in LDL cholesterol at doses of 20 and 10 mg, respectively. The most potent statins are those of the third generation, the so-called superstatins, which include rosuvastatin and pitavastatin [4, 5].

The aim of the study. The aim of the work is to study the evaluation of medication adherence among chronic coronary heart disease Moroccan patients using combination therapy with rosuvastatin.

The objectives of the study. Objectives of the work are the following:

1. To study the basic information about chronic coronary heart disease.
2. To study the impact of adherence on quality of Moroccan chronic coronary heart disease patient's life.
3. To study approaches to modern therapy of chronic coronary heart disease.
4. To analyze the opinions and beliefs of pharmacy visitors with chronic coronary heart disease concerning efficacy and safety of medication management.
5. To develop practical recommendations for physicians, pharmacists and patients about alternative ways to improve treatment adherences in Moroccan chronic coronary heart disease patients using rosuvastatin.

Object of research: medication adherence among chronic coronary heart disease Moroccan patients using combination therapy with rosuvastatin.

Subject of research: role of the factors contributing to medication adherence

among chronic coronary heart disease Moroccan patients using combination therapy with rosuvastatin.

Research methods. The methodological basis of the study is the principles of objectivity and consistency. The work uses a complex of general scientific and special methods: theoretical, generalization, data systematization, comparison, methods of studying literary sources, analysis, questionnaire method, statistical methods, etc.

Structure and scope of qualification work. Qualification work is presented on the 40 pages of typewritten text, consists of summary, introduction, 3 chapters, conclusions, references. The work is illustrated with 10 tables, 5 figures. The list of literature contains 31 references.

CHAPTER 1

MODERN PRESENTATION ABOUT CHRONIC CORONARY HEART DISEASE MANAGEMENT (LITERATURE REVIEW)

1.1. Role and place of statins in modern antiatherogenic therapy

Coronary heart disease (CHD) is a dynamic process of atherosclerotic plaque accumulation and functional changes in the coronary circulation, which can be reversed by lifestyle modification, pharmacological therapy and revascularization, leading to stabilization or regression of the disease. Thus, by influencing the dynamic process of plaque accumulation through the implementation of a primary or secondary preventive strategy, the risk of death due to CHD can be reduced. According to the WHO, over the past two decades (from 2000 to the end of 2019), mortality due to CHD has increased by 23.8% worldwide. CHD ranks first in the mortality structure in almost all high-economy countries, intermediate economies (intermediate high, intermediate low), except for low-economy countries, where infant mortality remains in first place, respiratory diseases in second place, and CHD in third place.

Statins are the drugs of choice for lowering the level of low-density lipoprotein cholesterol (LDL-C), which accumulates on the walls of blood vessels and leads to narrowing of their lumen and impaired blood flow. Statins inhibit the synthesis of endogenous cholesterol in hepatocytes by inhibiting the enzyme HMG-CoA reductase, which helps to reduce cholesterol synthesis in the liver and, by increasing the activity of LDL receptors on hepatocytes, reduces circulating low-density lipoprotein cholesterol [6].

There are several statins on the pharmaceutical market: atorvastatin, rosuvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, and pitavastatin (Table 1.1).

Table 1.1

Statins pharmaceutical market

Medicines	Middle dose, mg	Maximal dose, mg
Atorvastatin	10-20	80
Rosuvastatin	5-10	40
Simvastatin	10-20	40
Pravastatin	10-20	80
Lovastatin	20	40
Fluvastatin	20-40	80
Pitavastatin	1	4

All of the drugs presented are effective, but there are cases when some of them are even safer in terms of the development of side effects. Thus, an important advantage of rosuvastatin, fluvastatin, pravastatin, pitavastatin compared to other statins is that they are metabolized in the liver without the participation of cytochrome P450. This is important for reducing the risk of myopathy and rhabdomyolysis in case the patient needs to take certain drugs at the same time (for example, antifungals, antivirals, calcium channel antagonists) [6, 7].

It should be noted that the most studied statins are atorvastatin and rosuvastatin. These statins have demonstrated not only safety and high efficacy in reducing LDL-C levels, but also have shown a positive effect in preventing the development of repeated cardiovascular events.

The optimal dose of a statin depends on the patient's cardiovascular risk and the target LDL-C level that needs to be achieved to prevent cardiovascular complications.

According to the European guidelines, after cardiovascular risk stratification and determination of the target LDL-C level, the percentage reduction in LDL-C should be calculated and the statin and its dose selected to provide the necessary lipid-lowering effect should be selected. The degree of reduction in LDL-C depends

on the type and dose of the prescribed statin.

The American approach to choosing a statin and its dose is based on the principle of statin therapy intensity, which was developed based on calculating the average reduction in LDL-C required in patients with different cardiovascular risk factors, taking into account the lipid-lowering effect of different statins (Table 1.2).

Table 1.2

Statin therapy intensity

High-intensity therapy	Moderate-intensity therapy	Low-intensity therapy
↓LDL-C ≥50%	↓LDL-C 30-50%	↓LDL-C <30%
Rosuvastatin 20-40 mg Atorvastatin 40-80 mg	Rosuvastatin 5-10 mg Atorvastatin 10-20 mg Simvastatin 20-40 mg	Simvastatin 10 mg

If statin therapy is not effective enough, combination therapy using ezetimibe and PCSK9 inhibitors can be used (Table 1.3).

Table 1.3

Gradation of statin therapy intensity

Treatment Average	LDL reduction
Moderate-intensity statin	~ 30%
High-intensity statin	~ 50%
High-intensity statin + ezetimibe	~ 65%
PCSK9 inhibitor	~ 60%
PCSK9 inhibitor + High-intensity statin	~ 75%
PCSK9 inhibitor + High-intensity statin	~ 85%

High-intensity statin therapy is indicated for patients with [8-13]:

- documented cardiovascular disease (acute coronary syndrome, coronary artery disease, myocardial infarction in history, revascularization, stroke, transient

ischemic attack, peripheral artery disease);

- patients ≤75 years;
- patients with diabetes and high cardiovascular risk;
- LDL-C ≥4.9 mmol/L.

Moderate-intensity statin therapy is indicated for patients with:

- high cardiovascular risk
- patients with diabetes with moderate cardiovascular risk.

In other clinical cases, consider low-intensity statin therapy.

It should be noted right away that statins are not prescribed as a course for a specific period. The duration of statin therapy is determined by its effectiveness and safety. An indicator of the effectiveness of statin therapy is the reduction in LDL-C levels. Target LDL-C levels depend on the cardiovascular risk (CVR) of each individual patient: the higher the risk of developing adverse cardiovascular events, the lower the target LDL-C level should be (Table 1.4).

Table 1.4

Characteristics of the cardiovascular risk groups

CVR Group	Criteria	Target LDL level
Very high risk	documented CVD of atherosclerotic origin (clinically or according to angiography); SCORE≥10% SCORE2 and SCORE2-OP (< 50 years – ≥ 7.5%; 50-69 years – ≥ 10%; ≥ 70 years – ≥ 15%) familial hypercholesterolemia with confirmed CVD of atherosclerotic origin or other major risk factor; chronic kidney disease (GFR<30 ml/min); DM with target organ damage or ≥3 risk factors or early onset of type 1 DM with duration of >20 years.	<1.4 mmol/L or ≥50% decrease from baseline

Continued Table 1.4

High risk	SCORE 5-9%; SCORE2 and SCORE2-OP (< 50 years – 2.5 to < 7.5%; 50-69 years – 5 to < 10%; ≥ 70 years – 7.5 to < 15%) significant increase in the level of one of the listed risk factors (TC>8 mol/l or LDL-C>4.9 mmol/l or BP>180/110 mm Hg); familial hypercholesterolemia without additional risk factors; chronic kidney disease (GFR 30-59 ml/min); DM without target organ damage or DM with duration >10 years or another additional risk factor.	<1.8 mmol/L or ≥50% decrease from baseline
Intermediate risk	SCORE 1-4%; SCORE2 and SCORE2-OP (< 50 years – < 2.5%; 50-69 years – < 5%, ≥ 70 years -< 7.5%) young patients (for type 1 diabetes < 35 years; for type 2 diabetes < 50 years) with diabetes duration < 10 years without other additional risk factors.	<2.6 mmol/L
Low risk	SCORE <1% SCORE2 and SCORE2-OP (< 50 years – < 2.5%; 50-69 years – < 5%, ≥ 70 years -< 7.5%)	<3.0 mmol/L

Lipid profile should be assessed before starting statin therapy. However, in very high-risk patients and in case of development of, for example, acute myocardial infarction, ischemic stroke, statins should be prescribed regardless of the baseline LDL-C level. To monitor the effectiveness of statin therapy, periodic monitoring of

LDL-C level is recommended (every 4-12 weeks at the beginning of therapy, and after reaching the target LDL-C level - annually).

ALT is determined before starting statin therapy, as well as 8-12 weeks after starting therapy or in case of increasing the dose of statin. Long-term monitoring of ALT is not recommended, except in cases of symptoms of liver damage. In case of less than a 3-fold increase in ALT level, statin therapy should be continued with subsequent re-control of ALT level in 4-6 weeks. In case of more than 3-fold increase in ALT level, statin therapy should be suspended and rechecked in 4-6 weeks; statins can be re-administered with great caution only after normalization of ALT level [14, 15].

Before and during statin therapy, it is recommended to monitor ALT and creatine phosphokinase levels to identify patients for whom treatment is contraindicated and to detect side effects of statins.

Before prescribing statins, it is recommended to check the level of creatine phosphokinase, especially in patients at high risk of myopathy (e.g., elderly patients with comorbidities, patients with a history of muscle symptoms, patients taking drugs metabolized through the CYP enzyme system, patients with severe renal and hepatic disease). In case of more than 4-fold increase in the level of CK, statin therapy should be postponed. Routine monitoring of CK levels during statin therapy is not necessary, except in cases of symptoms of muscle damage or in patients at high risk of myopathy [13, 16].

If during statin therapy a patient is diagnosed with:

- more than 10-fold increase in CK level, discontinue treatment, check renal function and continue monitoring CK level every 2 weeks
- 4-10-fold increase in CK level without muscle symptoms, therapy can be continued, ensure monitoring of CK level every 2-6 weeks
- 4-10-fold increase in CK level with the appearance of muscle symptoms, discontinue treatment, continue monitoring of CK levels
- less than 4-fold increase in CK levels without muscle symptoms, continue

statin therapy, reassessment of CK levels in the dynamics

- less than 4-fold increase in CK levels with muscle symptoms, continue statin therapy, symptom control and reassessment of CK levels in the dynamics if symptoms persist, discontinue statin therapy, reassess symptoms in 6 weeks, and if they are absent, consider resuming statin therapy (choose another statin, prescribe a lower dose, change the frequency of administration, for example, every other day or 1-2 times a week).

If LDL-C levels are not sufficiently reduced, the statin regimen should be reviewed, increasing the statin dose to one that will allow achieving the target LDL-C level while being well tolerated by the patient.

Often, even under these conditions, it is not always possible to reduce LDL-C. Scientists most often associate this with the patient's genetic characteristics, which affect the body's sensitivity to the drug. In this case, it is recommended to strengthen lipid-lowering therapy by adding ezetimibe to the statin.

Statins are usually well tolerated by patients, however, in some cases side effects may occur, among which muscle symptoms in general and myopathy in particular are the most frequent.

Rhabdomyolysis is a very rare and dangerous side effect, occurring with a frequency of 1-3 cases per 100,000 patient-years. It is manifested by skeletal muscle pain, muscle necrosis, myoglobinuria and is always accompanied by a multiple increase in the level of creatine phosphokinase (CPK).

If a patient taking statins complains of muscle pain, a feeling of muscle stiffness, muscle weakness, but without an increase in the level of creatine phosphokinase, we can talk about statin-associated muscle symptoms. They occur in 10-15% of patients on statin therapy. In 2014, the National Lipid Association of the United States proposed a scale to assess the likelihood of statin-associated muscle symptoms in patients taking statins [17].

There are several approaches to treating these patients, including measuring CPK, using a clinical severity score, temporarily discontinuing statins and reintroducing other statins at the recommended or lower dose, and administering

statins every other day.

Elevated ALT levels occur in 0.5-2% of patients taking statins. This adverse effect is most often seen with high-dose statin therapy. A three-fold increase in ALT in 2 consecutive blood samples is clinically significant. A slight increase in ALT levels should not be considered a manifestation of statin hepatotoxicity. Moreover, routine monitoring of ALT levels during statin therapy is not currently recommended [18].

It is necessary to remember about the possibility of development of undesirable effects at simultaneous reception of statins with some medicines [18-21]. Most of statins, except rosuvastatin, fluvastatin, pitavastatin and pravastatin, are metabolized in a liver with participation of cytochrome P450. This has to be considered at simultaneous appointment of statins with other medicines which are metabolized with participation of the same enzyme system because of the increased risk of myopathy and rhabdomyolysis (Table 1.5).

Table 1.5

Interactions of statins with other groups of medicines

Anti-infectives	Calcium channel antagonists	Others
Itraconazole	Verapamil	Cyclosporine
Ketoconazole	Diltiazem	Danazol
Fluconazole	Amlodipine	Amiodarone
Erythromycin		Ranolazine
Clarithromycin		Grapefruit juice
Telithromycin		Gemfibrozil
HIV protease inhibitors		Nefazodone

Elderly patients are defined as patients over 65 years of age. According to current guidelines, statin therapy for secondary prevention in elderly patients is no different from statin therapy in younger patients. Statins for primary prevention of cardiovascular events are recommended for patients ≤75 years of age, regardless of

cardiovascular risk group. Statins for primary prevention in patients >75 years of age should be considered only if there is a high or very high cardiovascular risk. It should be noted that in elderly patients with significant renal impairment and/or potential risk of drug interactions, statins are prescribed initially at the minimum dose and then titrated to achieve target LDL-C values.

1.2. Characteristics of rosuvastatin

Statins are classified into three generations depending on their ability to reduce low-density lipoprotein cholesterol (LDL-C) and into two groups depending on their physicochemical properties. The first generation of statins entered the pharmaceutical market in the late 1980s–early 1990s. This generation is characterized by the lowest potency. The second generation – simvastatin and atorvastatin – had a higher potency, providing a 30% reduction in LDL-C at doses of 20 and 10 mg, respectively. The most potent are the third-generation statins – so-called superstatins, which include rosuvastatin and pitavastatin [3].

Based on their physicochemical properties and solubility, statins are divided into lipophilic and hydrophilic. Lipophilicity and hydrophilicity affect the absorption and excretion of drugs, as well as their entry into the cell. Thus, lipophilic substances immediately pass through cell membranes by passive diffusion, while hydrophilic ones require carrier molecules. Most statins are lipophilic; the only exceptions are rosuvastatin and pravastatin. The fact that lipophilic statins easily pass through cell membranes provides them with a greater potential for extrahepatic side effects, in particular from the muscles. In contrast, hydrophilic statins are hepatoselective, meaning their penetration into muscle tissue is much lower, and therefore the risk of side effects is lower. In addition, lipophilic statins more easily cross the blood-brain barrier and may therefore be associated with a higher risk of developing neurocognitive side effects [3, 22].

Most statins are metabolized by the cytochrome P450 system (atorvastatin, lovastatin, simvastatin – CYP3A4 isoform, fluvastatin – CYP2C9 isoform).

Pravastatin is mainly metabolized by sulfonation; in contrast, 90% of rosuvastatin undergoes biliary excretion unchanged, which provides this drug with a low potential for drug-drug interactions [22-24].

A large meta-analysis by H.G. Yebyo et al. (2019) involving 94,283 participants was devoted to comparing the effectiveness of different statins in the primary prevention of CVD. Rosuvastatin was found to have some of the best performance, including the ability to significantly reduce the number of nonfatal myocardial infarctions and nonfatal strokes (relative risk (RR) 0.72 (95% confidence interval (CI) 0.49-1.11 and 0.89 (95% CI 0.61-1.29), respectively), to reduce all-cause mortality (RR 0.88; 95% CI 0.63-1.23), and cardiovascular mortality (RR 0.91; 95% CI 0.61-1.35). Another systematic review and meta-analysis confirmed the high efficacy of rosuvastatin, revealing greater potency in reducing LDL-C for 40 mg of this drug compared with 80 mg of atorvastatin. According to the authors, high-intensity therapy with different statins is not equipotent, since According to the results obtained, and according to the pivotal VOYAGER study, rosuvastatin allows to achieve lower LDL-C values even when used in lower doses (compared to atorvastatin) [25].

The recent LODESTAR trial enrolled 4400 people with coronary heart disease who were treated with rosuvastatin or atorvastatin. LDL-C levels were consistently lower in the rosuvastatin group at 6 weeks, 3 and 6 months, 1 year, 2 and 3 years (all $p<0.001$) (Figure). The proportion of participants who achieved an LDL-C level <1.8 mmol/L was consistently higher in the rosuvastatin group than in the atorvastatin group: at 6 weeks, 62.9 vs. 54.6%, $p<0.001$; at 3 months, 66.7 vs. 58.8%, $p=0.02$; at 6 months, 64.3 vs. 53.1%, $p<0.001$; at 1 year, 61.5 vs. 53.1%, $p<0.001$; after 2 years– 64.0 vs. 57.2%, $p<0.001$; after 3 years–62.5 vs. 55.2%, $p<0.001$ [26].

A. Kumar et al. (2020) showed that, in addition to reducing LDL-C, rosuvastatin was on average 36% more effective than atorvastatin in reducing the total volume of atheromatous plaques, a marker of the total atherosclerotic burden. The studies included in the meta-analysis of these authors found a reduction in atheroma volume by 4.4-18.78% with rosuvastatin and only by 3.60-9.93% with

atorvastatin. Q. Ma et al. (2016) found the advantage of rosuvastatin over atorvastatin in reducing the content of C-reactive protein, a known predictor of cardiovascular events. On average, rosuvastatin reduced the content of C-reactive protein by 0.11 mg/L more potently than atorvastatin.

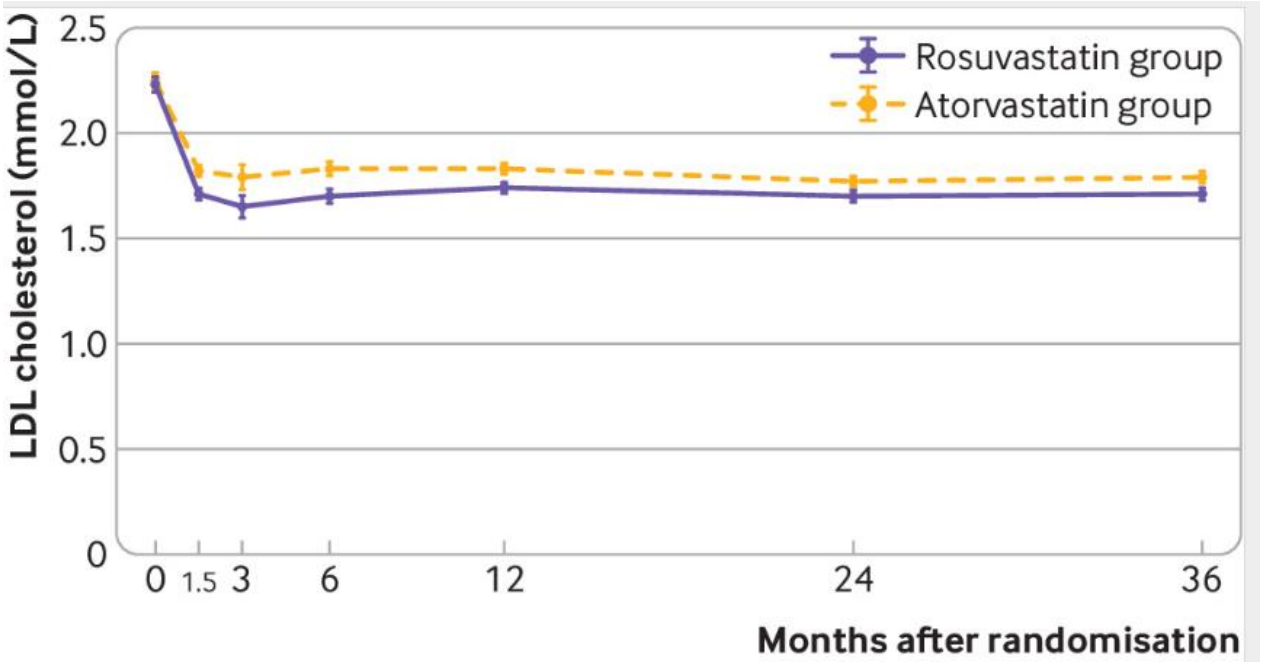

Fig. 1.1. LDL-C dynamics in the rosuvastatin and atorvastatin groups (Lee Y.-J. et al., 2023)

In patients with type 2 diabetes and dyslipidemia, rosuvastatin had a beneficial effect on the metabolic profile, which was manifested by a significant (compared to atorvastatin) decrease in glycated hemoglobin (by 9.13 vs. 2.35%), LDL-C (by 22.23 vs. 14.75%), triglycerides (by 13.56 vs. 8.21%), total cholesterol (by 16.10 vs. 10.81%), C-reactive protein (by 23.51 vs. 18.96%), and an increase in high-density lipoprotein cholesterol (by 2.5 vs. 0.21%) compared to baseline. The authors concluded that these statins are equivalent in their cardioprotective properties, but rosuvastatin is more effective in improving the lipid profile and atherogenic index, as well as in modulating the content of inflammatory biomarkers [27].

Statins, in particular rosuvastatin, have been described to have a number of

pleiotropic properties unrelated to LDL-C reduction, including improved endothelial function, reduced oxidative stress, stabilization of atherosclerotic plaques, immunomodulation, inhibition of vascular smooth muscle cell proliferation, effects on bone metabolism, anti-inflammatory effects, antithrombotic effects, reduced risk of dementia, etc. [28].

The JUPITER study (The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), which included >10,000 patients, found that rosuvastatin significantly reduced the number of new cancer cases and deaths from malignant neoplasms. The antitumor effect of statins is explained by their antiproliferative, antiangiogenic and proapoptotic effects [29].

J. Kim et al. (2019) studied the modulation of the intestinal microbiota of obese laboratory mice under the influence of statins, including rosuvastatin. Statin therapy significantly increased species biodiversity in the families *Bacteroides*, *Butyricimonas* and *Mucispirillum*, which was associated with a decrease in the inflammatory response in the intestine. It should be noted that the indicators of microbial biodiversity on the background of rosuvastatin were greater than on the background of atorvastatin. Interestingly, transplantation of the microbiota of mice treated with rosuvastatin into other mice reduced hyperglycemia in the latter. According to the authors, modulation of the microbiota is one of the important factors in the therapeutic effect of statins.

Rosuvastatin has been shown to have an effect on the genetics of gut microorganisms, including a decrease in the transport and metabolism of trimethylamine-N-oxide (a molecule of microbial origin associated with increased cardiovascular risk) and an increase in betaine and gamma-butyl betaine [30].

A cohort study by A. Israel et al. (2020) examined the protective effect of various statins and other medications on the incidence of hospitalizations for coronavirus disease (COVID-19). The authors collected demographic and clinical data from 10,295 adults hospitalized with COVID-19 and a matched control group, and used Fisher's exact test to assess the association between these data and the likelihood of hospitalization. The effects of most medications were neutral, but

background rosuvastatin was one of the few treatments that significantly reduced the likelihood of hospitalization (HR 0.673; 95% CI 0.596-0.758). A potential explanation for this finding is that SARS-CoV-2, like all RNA viruses, requires cholesterol molecules for entry into cells, assembly of new virions, and maintenance of structural stability, and rosuvastatin significantly reduces cholesterolemia [31].

It is known that a decrease in low-density lipoprotein cholesterol (LDL-C) by 1 mmol/l with these drugs leads to a decrease in the risk of death from all causes by 10%, coronary heart disease (CHD) by 20%, and all cardiac events by 16%. Thus, statin therapy is not only a decrease in the incidence of cardiovascular (CV) complications, but also prolongs life in the presence of a high CV risk.

Currently, cardiologists and therapists are well informed about who and how to prescribe statins, but ensuring that patients regularly take statins in adequate doses remains one of the most pressing problems.

Conclusions for chapter 1

1. The most important direction in the fight against CVD is the prevention and treatment of dyslipoproteinemias (DLP), which have a key pathogenetic importance in the development of atherosclerosis and its complications.

2. The results of numerous clinical studies indicate that the use of statins as primary and secondary prevention agents has a pronounced favorable effect on the prognosis, provides a significant reduction in morbidity and mortality from CVD.

3. Despite the awareness of general practitioners about the main provisions of clinical guidelines on the use of statins, many specific issues of their practical use in various clinical situations cause difficulties: from the choice of drug, dose, goal of therapy depending on the degree of cardiovascular risk (CVR) to monitoring the effectiveness and safety of statin therapy.

4. The global practice of using statins shows that the most frequently prescribed drugs are currently rosuvastatin and atorvastatin. This is due to the large evidence base of the effectiveness of these drugs, the breadth of indications and experience of their use in various clinical situations (acute coronary syndrome, chronic coronary syndrome, the period after a stroke or transient ischemic attack, diabetes, arterial hypertension, obliterative peripheral arterial disease, etc.).

CHAPTER 2
MATERIALS AND METHODS

The experimental part of the master thesis was conducted in collaboration with Pharmacie Chaouki (Ouled Mrah Sidi Aissa Centre Beni Mellal, Morocco).

The study was conducted in the period from August 12, 2023 to October 20, 2024. Our study included 30 pharmacy visitors who were diagnosed with chronic coronary heart disease and are using combination therapy with rosuvastatin.

For the purposes of the master thesis a questionnaire was developed for surveying of patients / pharmacy visitors with chronic coronary heart disease and are using combination therapy with rosuvastatin (table. 2.1.)

The questionnaire included questions of a general nature regarding the age, gender, as well as special questions related antiatherogenic therapy with rosuvastatin, medication adherence and quality of life. Particular attention was also paid to the assessment of criteria of efficacy and safety in such category of patients.

Materials were presented in hard copy, and there was also (optionally) an opportunity to take a Google Form survey.

Also, based on the results of the survey, practical recommendations for physicians, pharmacists and patients about alternative ways to improve antiatherogenic therapy adherences in Moroccan chronic coronary heart disease patients.

Based on the results of the study, practical recommendations were developed for Moroccan chronic coronary heart disease patients about antiatherogenic therapy with rosuvastatin.

The methodological basis of the study is the principles of objectivity and consistency. The work uses a complex of general scientific and special methods: theoretical, generalization, data systematization, comparison, methods of studying literary sources, analysis, questionnaire method, statistical methods, etc.

The data obtained from the experimental study were analyzed and stylistically processed and presented in the form of tables and diagrams to illustrate the results.

Table 2.1

Questionnaire for patients / pharmacy visitors with chronic coronary heart disease using combination therapy with rosuvastatin

1.	Sex and age	
2.	Smoking status: ex-smoker, non-smoker, passive smoker, active smoker?	
3.	How long have you had chronic coronary heart disease?	
4.	What are the main manifestations of this disease?	
5.	What comorbid, chronic diseases do you have?	
6.	What medications are you taking as part of combination therapy?	
7.	How long did you use rosuvastatin?	
8.	Which dose of rosuvastatin do you use?	
9.	What side effects did you experience most often while using rosuvastatin?	
10.	Do you follow the rules for rational prescribing of medicines?	
11.	How often do you see your doctor and monitor your condition?	
12.	What laboratory tests do you usually monitor to control the efficacy of rosuvastatin therapy?	
13.	What laboratory tests do you usually monitor to control the safety of rosuvastatin therapy?	
14.	Does this disease affect your quality of life?	
15.	What is the pharmacist's role in improving the efficacy and safety of drug therapy with rosuvastatin?	

Conclusions for chapter 2

1. The experimental part of the master thesis was conducted in collaboration with Pharmacie Chaouki (Ouled Mrah Sidi Aissa Centre Beni Mellal, Morocco). For the purposes of the survey were pooled 30 pharmacy visitors with chronic coronary heart disease and are using combination therapy with rosuvastatin.

2. The questionnaire included questions of a general nature regarding the age, gender, as well as special questions related antiatherogenic therapy with rosuvastatin, medication adherence and quality of life. Particular attention was also paid to the assessment of criteria of efficacy and safety in such category of patients.

CHAPTER 3

EVALUATION OF MEDICATION ADHERENCE AMONG CHRONIC CORONARY HEART DISEASE MOROCCAN PATIENTS USING COMBINATION THERAPY WITH ROSUVASTATIN (EXPERIMENTAL PART)

3.1. Survey of Moroccan pharmacy visitors concerning atherosclerosis management with rosuvastatin

The total number of surveyed pharmacy visitors was 30. The inclusion criteria were: diagnosis with chronic coronary heart disease, use of rosuvastatin; volunteering to take part in the survey.

The main characteristics of the surveyed pharmacy visitors are presented in the table 3.1.

Table 3.1

Characteristics of surveyed pharmacy visitors with asthma

#	Patients characteristics	Indicator	% from total amount
1.	Sex		
	Female	10	33.33
	Male	20	66.67
2.	Minimal age, years	48	
3.	Maximal age, years	83	
4.	Smoking patients	5	16.67
5.	Experience of rosuvastatin therapy	30	100

From all surveyed pharmacy visitors, 10 were females (33.33%) and 20 were male (66.67%). The average age was 65.5, the youngest respondent was 48 years old

and the oldest – 83 years old. 5 % of pharmacy visitors were smoking persons with chronic coronary heart disease. From the surveyed pharmacy visitors, 100 % experienced rosuvastatin therapy.

Characteristics of chronic coronary heart disease patients according to rosuvastatin medications are presented in Table 3.2.

Table 3.2

Patients with chronic coronary heart disease according to rosuvastatin use

Type of statins therapy	Dose of rosuvastatin	Indicator	% from total amount
Middle-intensity statin therapy	5	2	6.67
	10	10	33.33
High-intensity statin therapy	20	15	50.00
	40	3	10.00

The most significant laboratory parameters are lowering LDL cholesterol and total cholesterol and increasing HDL cholesterol and lowering triglycerides.

Normal ranges of Lipid Panel:

– total cholesterol: 5 mmol/L or below;
– LDL cholesterol: 3 mmol/L or below;
– HDL cholesterol: 1 mmol/L or above (for men) and 1.2 mmol/L or above (for women);
– fasting triglycerides: 1.7 mmol/L or below;
– non-fasting triglycerides: 2.3 mmol/L or below.

Among our respondents, 24 people (80%) understand the importance of laboratory control of results and constantly monitor these indicators, and only 6 respondents (20%) do not attach due importance to this process.

The results are presented at Fig. 3.1.

As part of our research, we also investigated the awareness of our respondents about the normal range of the laboratory indicators they monitor. We found out that out of 24 respondents who monitor laboratory parameters, 20 people (83%) know the

norms of these parameters.

Usually, our respondents visit their doctor twice a year (this was the most popular answer during the survey) and usually during this period they also visit the laboratory.

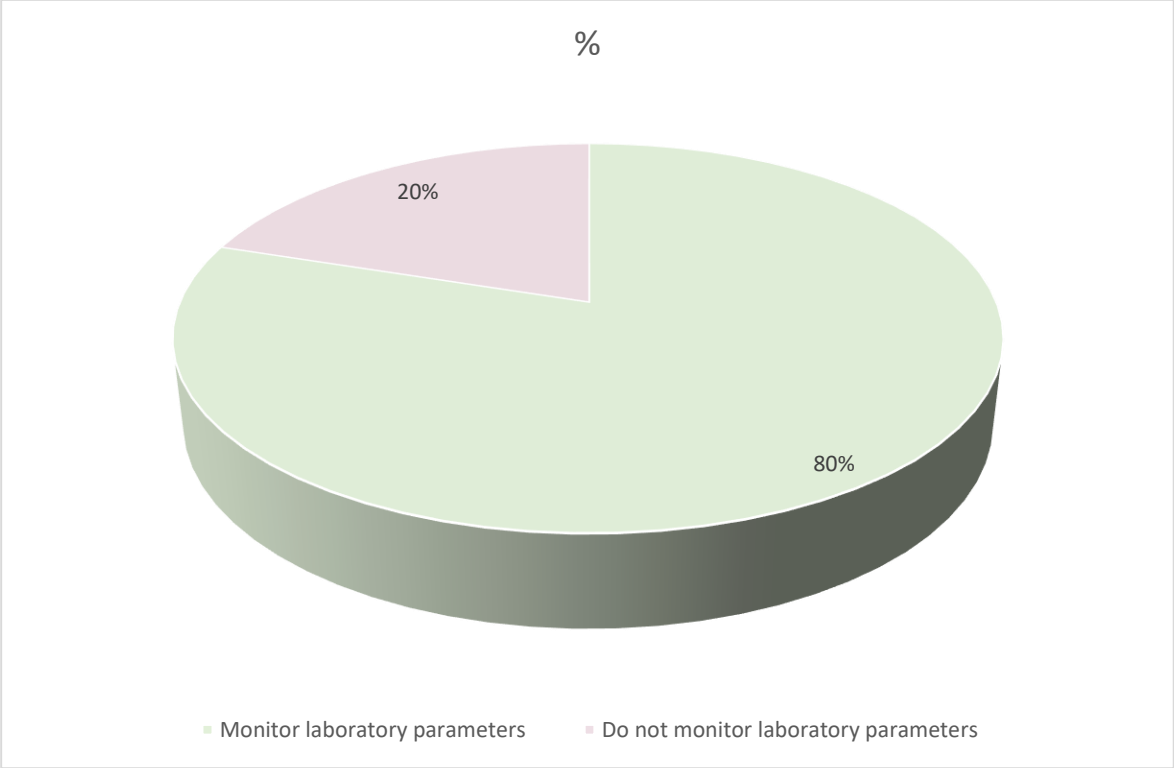

Fig. 3.1. Characteristics of respondents about monitoring laboratory parameters

We analyzed laboratory parameters in three respondents before treatment with rosuvastatin and several months after treatment. The results are presented in the Table 3.3.

The data presented in Table 3.3 demonstrate that all study subjects had a clear tendency to decrease/normalize their lipid parameters on rosuvastatin treatment. In Patient 2 and Patient 3, the majority of lipid profile parameters reached normal values.

Thus, the presented results indicate the presence of objective reliable criteria for the effectiveness of treatment with rosuvastatin-based drugs.

Table 3.3

Analysis of lipid profile under rosuvastatin use

Laboratory tests	Patient 1 (male)		Patient 2 (female)		Patient 3 (male)	
	before	after	before	after	before	after
total cholesterol, mmol/L	8.7	5.3	6.3	4.6	7.0	4.9
LDL cholesterol, mmol/L	5.3	3.2	4.2	2.7	3.9	2.6
HDL cholesterol, mmol/L	2.2	1.3	1.7	1.2	1.8	0.9
fasting triglycerides, mmol/L	2.3	1.9	1.9	1.6	1.8	1.4

In the course of the study, we also found out the most common side effects that occurred with the use of rosuvastatin-containing drugs. We also asked how these negative effects affected the quality of life of our respondents.

Our respondents named the following side effects:

– headache: 12 respondents (40.00 %);
– constipation, nausea, abdominal pain: 10 respondents (33.33 %);
– myalgia, rhabdomyolysis: 8 respondents (26.67 %);
– allergic reactions: 3 respondents (10.00 %);
– diabetes mellitus: 1 respondent (3.00 %).

The frequency of diabetes mellitus depends on the presence of risk factors (fasting glucose $\geqslant$ 5.6 mmol/L, BMI > 30 kg/m^2, elevated triglyceride levels, history of arterial hypertension).

As with other HMG-CoA inhibitors, the incidence of adverse reactions tends to be dose-dependent.

The results are presented at Fig. 3.2.

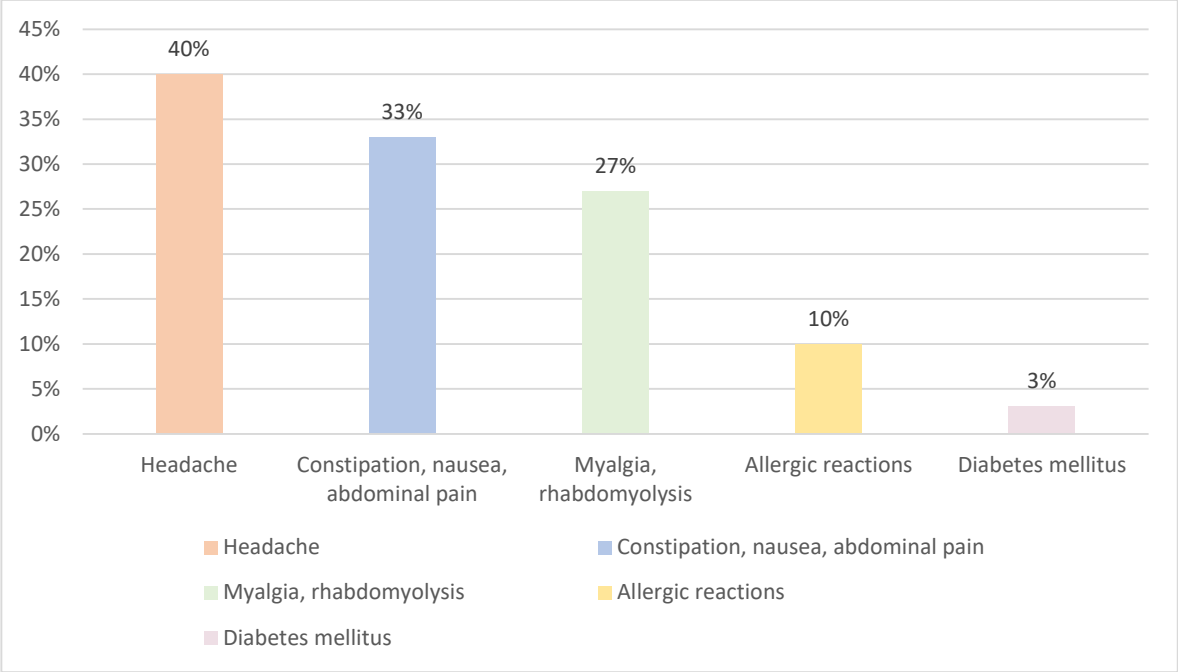

Fig. 3.2. The main side effects of rosuvastatin

One of the key methods of combating high cholesterol is to follow a proper diet. A hypocholesterol diet is aimed at reducing the consumption of saturated fats, trans fats and cholesterol, which can contribute to the formation of plaque in blood vessels. This diet is based on foods rich in fiber (vegetables, fruits, whole grains), lean protein sources (fish, poultry, legumes), and healthy fats found in olive oil, nuts, and seeds.

When following a hypocholesterol diet, it is important to avoid fried foods, limit the consumption of fast food, sausages, fatty dairy products, and confectionery. It is also recommended to replace fatty meats with lean counterparts and include foods that help reduce “bad” cholesterol, such as avocados, flaxseed, and oily fish.

A cholesterol-lowering diet is not only a way to lower cholesterol, but also helps to improve overall health, reduce the risk of cardiovascular disease, and

maintain an optimal weight.

In our study, we asked our respondents to what extent they adhere to a hypocholesterol diet. So, according to the survey results, we found the following picture: 50 % of respondents follow the diet all the time, 25 % do so from time to time, and 25 % do not pay due attention to this issue.

The results are presented at Fig. 3.3.

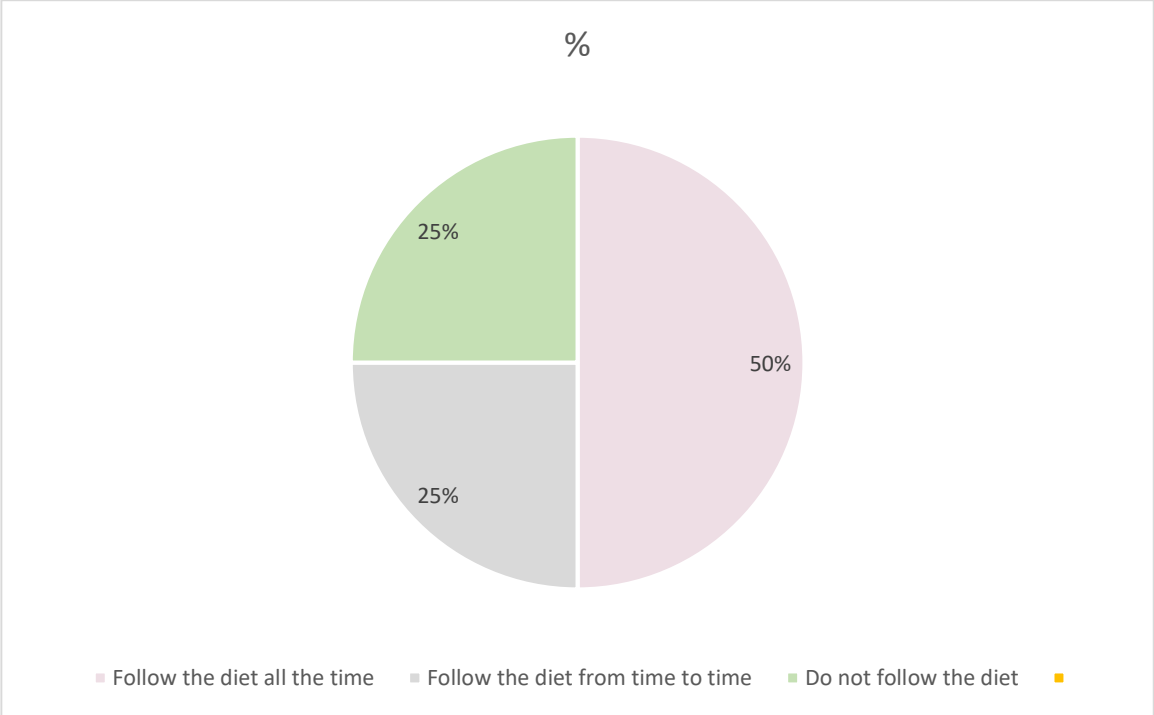

Fig. 3.3. Following the diet by the respondents

Therefore, as part of the pharmaceutical care in the pharmacy of this category of visitors, we focused their attention on this issue, since diet is a significant indicator that positively affects the effect of antiatherogenic therapy.

One of the aspects that we paid due attention to was the interaction of rosuvastatin with other medicines as part of combination therapy in our respondents.

In the course of the study, we found evidence of both pharmacodynamic and pharmacokinetic drug interactions. The most significant interactions are listed in the Table 3.4.

Table 3.4

Interactions of rosuvastatin with other drugs

Drugs	Result of interaction
Ezetimibe	the use of rosuvastatin/ezetimibe combination therapy allows for effective control of LDL cholesterol levels in patients with dyslipidemia, has a neutral effect on glucose metabolism, provides a favorable safety profile, and stabilization and regression of atherosclerotic plaques
Gemfibrozil, fenofibrate, other fibrates and lipid-lowering doses (⩾ 1 g/day) of niacin (nicotinic acid)	increase the risk of myopathy when used concomitantly with HMG-CoA inhibitors, presumably due to the fact that they can cause myopathy when used alone. A dose of 40 mg is contraindicated in concomitant use of fibrates. Such patients should also start therapy with a dose of 5 mg.
Antacids	the simultaneous use of rosuvastatin with antacid suspensions containing aluminum or magnesium hydroxide reduced the concentration of rosuvastatin in the blood plasma by approximately 50%. This effect was less pronounced when taking antacids 2 hours after rosuvastatin
Erythromycin	the simultaneous use of rosuvastatin and erythromycin reduced rosuvastatin AUC by 20% and Cmax by 30%. This interaction may be caused by increased intestinal motility due to the action of erythromycin.
Ticagrelor	Ticagrelor may affect the renal excretion of rosuvastatin, increasing the risk of its accumulation. The combined use of ticagrelor and rosuvastatin led to a decrease in renal function, increased creatine kinase levels, and rhabdomyolysis.

Ezetimibe is a representative of a new class of lipid-lowering agents that selectively inhibit intestinal absorption of cholesterol by a mechanism of action different from other cholesterol-lowering drugs. The properties of the drug include the following:

– inhibition of cholesterol absorption without affecting the absorption of TG, fatty and bile acids, progesterone, ethinylestradiol and fat-soluble vitamins A and D;

– promoting the reduction of the amount of cholesterol entering the liver;

– activation of LDL receptors by enhancing the clearance of LDL cholesterol from the blood.

At the final stage of the study, we assessed the adherence to treatment of our respondents. Thus, according to a number of criteria (both subjective and objective), we found that 24 respondents (80%) showed a fairly high level of adherence to the treatment. and only 20% had an average level of adherence, as they did not take into account a number of important recommendations regarding non-pharmacological and pharmacological treatment with rosuvastatin-containing drugs.

The results are presented at Fig. 3.4.

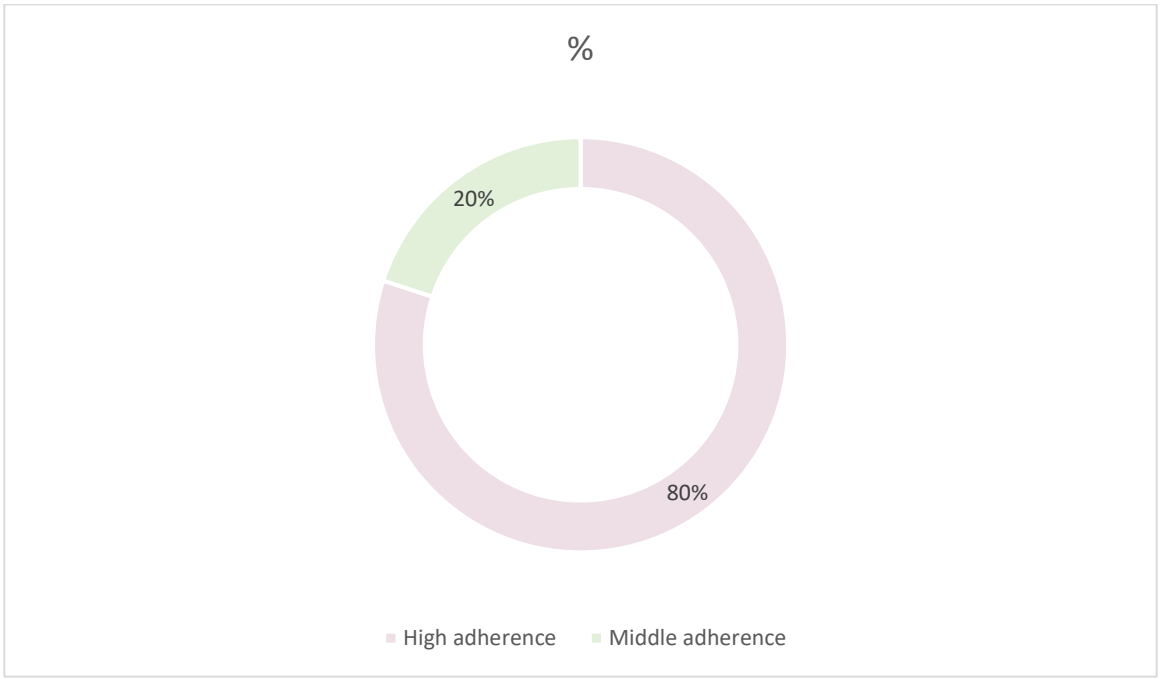

Fig. 3.4. treatment adherence of the respondents

One of the most important factors that directly affects patient outcomes is adherence to treatment. This therapeutic parameter is defined as the level of patient compliance with recommended treatment and involves the shared responsibility of both the patient and the physician.

A good option for improving adherence is a combined approach to increasing patient attention to medication therapy, which consisted of the following factors:

– active counseling by pharmacists and monitoring of medication dispensing;
– educational programs for patients;
– interaction between pharmacists and primary care physicians;
– reminder messages.

Therefore, the issue of adherence to treatment in patients with high cardiovascular risk requires widespread discussion and further study, and some methods for improving it should already be mastered and actively implemented in clinical practice.

3.2. Discussion of the obtained results

Cardiovascular diseases (CVD) are the leading cause of death and disability worldwide, leading to more than 18.5 million deaths per year, with CHD causing half of them, and 88% of CHD deaths are due to metabolic risk factors. Among them, the impact of elevated levels of low-density lipoprotein cholesterol (LDL-C) plays a causal role in ~44% of cases. Lifestyle changes combined with rapid population aging are leading to an increase in the number of people more susceptible to CVD. These include patients with hypercholesterolemia, a pathological condition in which the level of cholesterol in the blood exceeds 5.2 mmol/L. Excessive cholesterol increases the risk of developing atherosclerosis and serious CVD – arterial hypertension (AH), coronary heart disease (CHD), myocardial infarction (MI), and stroke.

Hypercholesterolemia is usually caused by excessive intake of fats in the body

against the background of their slow breakdown, physical inactivity, lack of physical activity, and a sedentary lifestyle. Hypercholesterolemia can also be familial, i.e., develop as a result of a burdened heredity.

Dyslipidemia is one of the most important modifiable risk factors for CVD. Genetic, epidemiologic, and clinical studies have established a causal relationship between elevated LDL cholesterol levels and a higher likelihood of CVD. Clinical and genetic studies have shown that lowering LDL-C reduces the risk of cardiovascular (CV) events, regardless of the mechanism by which this result is achieved. In addition, the greater the reduction in LDL-C concentration, the greater the clinical benefit.

Treatment of hypercholesterolemia is much more effective today than it was ten years ago. After all, in addition to the main drugs used for this purpose - statins - new therapeutic approaches are available that have expanded the possibilities of lowering lipid levels.

According to the recommendations for the treatment of dyslipidemias, lifestyle changes, normalization of nutrition and sufficient physical activity are mandatory. The main goal of treatment is to achieve target LDL cholesterol levels.

Treatment should begin with lifestyle modifications:

– smoking cessation;
– weight loss, if necessary;
– increase in physical activity;
– reducing the consumption of saturated fats and trans fats, while increasing the consumption of poly- and monounsaturated fats, etc.

If these lifestyle measures are not sufficient, drug therapy should be initiated. The drugs of choice are statins, as well as ezetimibe in combination with statins. The effectiveness of such treatment has been proven in randomized clinical trials.

According to the guidelines of the European Society of Cardiology and the European Atherosclerosis Society (ESC/EAC, 2019), treatment should be prescribed taking into account the likelihood of developing CV events of atherosclerotic origin, which reflects the combined effect of a number of risk factors on the assessment of

its degree.

The efficacy and good tolerability of rosuvastatin, a hydrophilic statin with high hepatoselectivity, is due to its low systemic bioavailability (and therefore low risk of myotoxicity) and minimal involvement in the metabolism of the cytochrome P450 system.

The experimental part of the master thesis was conducted in collaboration with Pharmacie Chaouki (Ouled Mrah Sidi Aissa Centre Beni Mellal, Morocco). For the purposes of the survey were pooled 30 pharmacy visitors with chronic coronary heart disease and are using combination therapy with rosuvastatin.

From all surveyed pharmacy visitors, 10 were females (33.33%) and 20 were male (66.67%). The average age was 65.5, the youngest respondent was 48 years old and the oldest – 83 years old. 5 % of pharmacy visitors were smoking persons with chronic coronary heart disease. From the surveyed pharmacy visitors, 100 % experienced rosuvastatin therapy.

Among our respondents, 24 people (80%) understand the importance of laboratory control of results and constantly monitor these indicators, and only 6 respondents (20%) do not attach due importance to this process.

We found out that out of 24 respondents who monitor laboratory parameters, 20 people (83%) know the norms of these parameters.

Usually, our respondents visit their doctor twice a year (this was the most popular answer during the survey) and usually during this period they also visit the laboratory.

We also found out the most common side effects that occurred with the use of rosuvastatin-containing drugs. We also asked how these negative effects affected the quality of life of our respondents.

Our respondents named the following side effects: headache: 12 respondents (40.00 %); constipation, nausea, abdominal pain: 10 respondents (33.33 %); myalgia, rhabdomyolysis: 8 respondents (26.67 %); allergic reactions: 3 respondents (10.00 %); diabetes mellitus: 1 respondent (3.00 %).

In our study, we asked our respondents to what extent they adhere to a

hypocholesterol diet. So, according to the survey results, we found the following picture: 50 % of respondents follow the diet all the time, 25 % do so from time to time, and 25 % do not pay due attention to this issue.

At the final stage of the study, we assessed the adherence to treatment of our respondents. Thus, according to a number of criteria (both subjective and objective), we found that 24 respondents (80%) showed a fairly high level of adherence to the treatment. and only 20% had an average level of adherence, as they did not take into account a number of important recommendations regarding non-pharmacological and pharmacological treatment with rosuvastatin-containing drugs.

Thus, correction of dyslipidemia with statins has been a cornerstone of CVD prevention for several decades. Since most patients require long-term (lifelong) statin therapy, the issue of adherence to these medications is extremely important.

3.3. Practical recommendations for the rational use of statins (rosuvastatin)

Cardiovascular diseases are the leading cause of mortality in the world. Statins, as inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, are the mainstay of dyslipidemia treatment to to reduce cardiovascular risk. Dyslipidemia is one of the key risk factors for atherosclerosis and its complications, including coronary heart disease (CHD) and cerebral stroke.

Reducing LDL cholesterol levels is the main objective of therapy with lipid-lowering drugs. Statins, as HMG-CoA reductase inhibitors, are the mainstay of dyslipidemia treatment due to their ability to block the synthesis of cholesterol synthesis in the liver and increase the activity of LDL receptors.

One of the most powerful statins widely used to lower blood lipids is rosuvastatin. Its effectiveness has been confirmed by numerous clinical trials that have demonstrated a significant reduction in low-density lipoprotein (LDL) levels, an increase in high-density lipoprotein (HDL) levels, as well as an effect on other components of the atherogenic lipid profile. Due to its pronounced hypolipidemic

effect and pleiotropic properties, rosuvastatin is the drug of choice for patients with dyslipidemia and and high risk of cardiovascular complications, it can cause regression of the atherosclerotic process and is effective for primary and secondary prevention of cardiovascular events.

Rosuvastatin provides a significant and predictable reduction in LDL cholesterol in a dose-dependent manner. Its features include:

- high selectivity for liver cells;
- long half-life (nearly 19 hours);
- low susceptibility to metabolism through the cytochrome P450.

Rosuvastatin is a fully synthetic inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and has a dose-dependent pharmacokinetics. Its absolute bioavailability is approximately 20%. Rosuvastatin acts by competitively inhibiting the enzyme HMG-CoA reductase, which is key in cholesterol synthesis, which leads to a decrease in intracellular cholesterol levels and stimulates the expression of LDL receptors on the surface of hepatocytes. The result is:

- reducing the level of LDL, the main fraction of atherogenic lipoproteins;

- decrease in the level of apolipoprotein B, the main structural protein of atherogenic particles;

- reducing the level of triglycerides;

- increasing the level of HDL.

Thus, rosuvastatin not only reduces the level of atherogenic lipids, but also helps to reduce the progression of atherosclerosis.

The recommended initial dose is 5mg or 10mg orally once daily for patients who have not previously used statins and those who have been switched to rosuvastatin from another HMG-CoA reductase inhibitor. When selecting the initial dose, the cholesterol level of each individual patient and the risk of cardiovascular disorders in the future, as well as the likelihood of adverse reactions, should be taken into account. If necessary, the dose can be increased to the next level after 4 weeks (see Pharmacodynamics). Given that adverse reactions occur more often with a dose of 40 mg than with lower doses, the final titration of the dose to 40 mg should be

made only in patients with severe hypercholesterolemia and a high risk of cardiovascular disorders (in particular in patients with familial hypercholesterolemia), who failed to achieve the goal of treatment with a dose of 20 mg and who will be under regular observation. At the beginning of taking the drug at a dose of 40 mg, specialist supervision is recommended.

The recommended initial dose for patients aged > 70 years is 5 mg. No other age-related dose adjustment is required.

No dose adjustment is required in patients with mild to moderate renal impairment.

The recommended initial dose for patients with moderate renal impairment (creatinine clearance < 60 mL/min) is 5 mg. A dose of 40 mg is contraindicated in patients with moderate renal impairment. The use of rosuvastatin in patients with severe renal impairment is contraindicated in any dose.

The drug is contraindicated during pregnancy or lactation.

Women of childbearing age should use appropriate contraception.

Rosuvastatin, like other HMG-CoA reductase inhibitors, should be administered with caution to patients with factors that cause myopathy/rhabdomyolysis.

These factors include:

- renal dysfunction;
- hypothyroidism;
- a history of hereditary muscle diseases in the individual or family history;
- a history of myotoxicity with other HMG-CoA reductase inhibitors or fibrates;
- alcohol abuse;
- age > 70 years;
- situations that may lead to an increase in the level of rosuvastatin in the blood plasma;
- simultaneous use of fibrates.

Contraindications:

- hypersensitivity to rosuvastatin or to any other components of the drug;
- liver disease in the active phase, including a persistent increase in serum transaminases of unknown etiology and any increase in serum transaminases that is 3 times higher than the upper limit of normal;
- severe renal dysfunction (creatinine clearance < 30 ml/min);
- myopathy;
- simultaneous use with cyclosporine;
- pregnancy or lactation. The drug is contraindicated in women of reproductive age who do not use proper contraception.

A dose of 40 mg is contraindicated in patients with a predisposition to myopathy/rhabdomyolysis. Risk factors may include:

- moderate renal impairment (creatinine clearance < 60 ml/min)
- hypothyroidism;
- a history of hereditary muscle diseases in an individual or family history;
- history of myotoxicity caused by the use of other HMG-CoA reductase inhibitors or fibrates;
- alcohol abuse;
- situations that may lead to an increase in the concentration of rosuvastatin in the blood plasma;
- patients belonging to the Mongoloid race;
- concomitant use of fibrates.

Conclusions for chapter 3

1. The experimental part of the master thesis was conducted in collaboration with Pharmacie Chaouki (Ouled Mrah Sidi Aissa Centre Beni Mellal, Morocco). For the purposes of the survey were pooled 30 pharmacy visitors with chronic coronary heart disease and are using combination therapy with rosuvastatin.

2. Among our respondents, 24 people (80%) understand the importance of laboratory control of results and constantly monitor these indicators, and only 6 respondents (20%) do not attach due importance to this process. We found out that out of 24 respondents who monitor laboratory parameters, 20 people (83%) know the norms of these parameters.

3. The most typical side effects were: headache: 12 respondents (40.00 %); constipation, nausea, abdominal pain: 10 respondents (33.33 %); myalgia, rhabdomyolysis: 8 respondents (26.67 %); allergic reactions: 3 respondents (10.00 %); diabetes mellitus: 1 respondent (3.00 %).

4. 50 % of respondents follow the diet all the time, 25 % do so from time to time, and 25 % do not pay due attention to this issue. 24 respondents (80%) showed a fairly high level of adherence to the treatment. and only 20% had an average level of adherence, as they did not take into account a number of important recommendations regarding non-pharmacological and pharmacological treatment with rosuvastatin-containing drugs.

5. Medical, pharmaceutical specialists and also patients should be involved in the pharmacotherapy process with rosuvastatin-based medicines, which will positively impact the effectiveness and safety indicators of the therapy for this disease.

CONCLUSIONS

1. Atherosclerosis is a chronic pathological condition that underlies most cardiovascular diseases. The high efficacy of statins in the primary and secondary prevention of cardiovascular diseases has been confirmed by numerous clinical studies. Rosuvastatin is one of the most effective and safety statins mowdays.

2. Among our respondents, 24 people (80%) understand the importance of laboratory control of Lipid profile and constantly monitor these indicators, and only 6 respondents (20%) do not attach due importance to this process. We found out that out of 24 respondents who monitor laboratory parameters, 20 people (83%) know the norms of these parameters.

3. The most typical side effects of rosuvastatin-based medicines were: headache: 12 respondents (40.00 %); constipation, nausea, abdominal pain: 10 respondents (33.33 %); myalgia, rhabdomyolysis: 8 respondents (26.67 %); allergic reactions: 3 respondents (10.00 %); diabetes mellitus: 1 respondent (3.00 %).

4. 50 % of respondents follow the diet all the time, 25 % do so from time to time, and 25 % do not pay due attention to this issue. 24 respondents (80%) showed a fairly high level of adherence to the treatment. and only 20% had an average level of adherence, as they did not take into account a number of important recommendations regarding non-pharmacological and pharmacological treatment with rosuvastatin-containing drugs.

5. Medical, pharmaceutical specialists and also patients should be involved in the pharmacotherapy process with rosuvastatin-based medicines, which will positively impact the effectiveness and safety indicators of the therapy for this disease.

REFERENCES

1. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines / S. S. Virani et al. *J Am Coll Cardiol*. 2023. Vol. 82(9). P. 833-955.

2. Investigating the effect of education on health literacy and its relation to health-promoting behaviors in health center / T. Bayati et al. *J Educ Health Promot*. 2018. Vol. 7. P. 127.

3. Hussain A., Kaler J., Ray S. D. The Benefits Outweigh the Risks of Treating Hypercholesterolemia: The Statin Dilemma. *Cureus*. 2023. Vol. 15(1). P. e33648.

4. Egom E. E., Hafeez H. Biochemistry of Statins. *Adv Clin Chem*. 2016. Vol. 73. P. 127-68.

5. State of the art comprehensive review of individual statins, their differences, pharmacology, and clinical implications / V. Azemawah et al. *Cardiovasc Drugs Ther*. 2019. Vol. 33(5). P. 625-639.

6. Statin Medications / O. Sizar et al. Treasure Island (FL) : StatPearls Publishing, 2025. URL: https://pubmed.ncbi.nlm.nih.gov/28613690/ (Date of access: 15.02.2025).

7. Uptitration of statin therapy in women and men: a population-based cohort study / P. Kiss et al. *Eur Heart J Qual Care Clin Outcomes*. 2025. Vol. 17. P. qcaf017.

8. High-Intensity Statins Benefit High-Risk Patients: Why and How to Do Better / S. M. Grundy et al. *Mayo Clin Proc.* 2021. Vol. 96(10). P. 2660-2670.

9. Alternative ldl cholesterol-lowering strategy vs high-intensity statins in atherosclerotic cardiovascular disease: a systematic review and individual patient data meta-analysis / Y. J. Lee et al. *JAMA Cardiol.* 2025. Vol. 10(2). P. 137-144.

10. Association between the intensity of statin therapy and physical activity 1 year after acute coronary syndrome: a multicentre prospective cohort study in Switzerland / A. Boudon et al. *BMJ Open*. 2025. Vol. 15(1). P. e088262.

11. Effects of statin therapy on diagnoses of new-onset diabetes and worsening

glycaemia in large-scale randomised blinded statin trials: an individual participant data meta-analysis / Cholesterol Treatment Trialists' et al. *Lancet Diabetes Endocrinol.* 2024. Vol. 12(5). P. 306-319.

12. The clinical effectiveness and safety of low/moderate-intensity statins & ezetimibe combination therapy vs. high-intensity statin monotherapy: a systematic review and meta-analysis / P. Sydhom et al. *BMC Cardiovasc Disord.* 2024. Vol. 24(1). P. 660.

13. **13=17.** Statin-induced liver injury patterns: a clinical review / L. D. Averbukh et al. *J Clin Transl Hepatol*. 2022. Vol. 10(3). P. 543-552.

14. Association of statin use with risk of liver disease, hepatocellular carcinoma, and liver-related mortality / M. S. Vell et al. *JAMA Netw Open*. 2023. Vol. 6(6). P. e2320222.

15. Khatiwada N., Hong Z. Potential benefits and risks associated with the use of statins. *Pharmaceutics*. 2024. Vol. 16(2). P. 214.

16. Cheon D. Y., Jo S. H. Adverse effects of statin therapy and their treatment. *Cardiovasc Prev Pharmacother*. 2022. Vol. 4(1). P. 1-6.

17. Side effects of statins: from pathophysiology and epidemiology to diagnostic and therapeutic implications / M. Ruscica et al. *Cardiovasc Res*. 2023. Vol. 118(17). P. 3288-3304.

18. Patel K. K., Sehgal V. S., Kashfi K. Molecular targets of statins and their potential side effects: Not all the glitter is gold. *Eur J Pharmacol*. 2022. Vol. 922. P. 174906.

19. Zhou J., Yu L., Xu H. A systematic review of the drug-drug interaction between Statins and Quinolones. *BMC Pharmacol Toxicol*. 2024. Vol. 25(1). P. 39.

20. Bellosta S., Corsini A. Statin drug interactions and related adverse reactions: an update. *Expert Opin Drug Saf*. 2018. Vol. 17(1). P. 25–37.

21. Hirota T., Fujita Y., Ieiri I. An updated review of pharmacokinetic drug interactions and pharmacogenetics of statins. *Expert Opin Drug Metab Toxicol*. 2020. Vol. 16(9). P. 809–22.

22. Climent E., Benaiges D., Pedro-Botet J. Hydrophilic or lipophilic statins? *Front Cardiovasc Med*. 2021. Vol. 8. P. 687585.

23. Ramkumar S., Raghunath A., Raghunath S. Statin therapy: review of safety and potential side effects. *Acta Cardiol Sin*. 2016. Vol. 32(6). P. 631-639.

24. Egom E. E., Hafeez H. Biochemistry of Statins. *Adv Clin Chem*. 2016. Vol. 73. P. 127-68.

25. Comparative efficacy and safety among high-intensity statins. Systematic Review and Meta-Analysis / M. Jaam et al. *J Comp Eff Res*. 2023. Vol. 12(3). P. e220163.

26. Rosuvastatin versus atorvastatin treatment in adults with coronary artery disease: secondary analysis of the randomised lodestar trial / Y. J. Lee et al. *BMJ* 2023. Vol. 383. P. e075837.

27. Werida R., Khairat I., Khedr N. F. Effect of atorvastatin versus rosuvastatin on inflammatory biomarkers and LV function in type 2 diabetic patients with dyslipidemia. *Biomed Pharmacother*. 2021. Vol. 135. P. 111179.

28. Pleotropic effects of statins: the dilemma of wider utilization of statin / A. Choudhary et al. *Egypt Heart J*. 2023. Vol. 75(1). P. 1.

29. The association of statin therapy and cancer: a meta-analysis / Z. Chen et al. *Lipids Health Di*s. 2023. Vol. 22(1). P. 192.

30. Rosuvastatin alters the genetic composition of the human gut microbiome / M. Kummen et al. *Sci Rep.* 2020. Vol. 10. P. 5397.

31. The use of statins was associated with reduced COVID-19 mortality: a systematic review and meta-analysis / K. S. Wu et al. *Ann Med*. 2021. Vol. 53(1). P. 874-884.

Ф А 2.2.1–32-366

National University of Pharmacy

Faculty pharmaceutical
Department of clinical pharmacology and clinical pharmacy

Level of higher education master

Specialty 226 Pharmacy, industrial pharmacy
Educational and professional program Pharmacy

APPROVED
Head of Department
of Pharmacology and
Clinical Pharmacy

Sergii SHTRYGOL`
«02» of September 2024

ASSIGNMENT
FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

Omar ELKADIRI

1. Topic of qualification work: «Evaluation of medication adherence among chronic coronary heart disease Moroccan patients using combination therapy with rosuvastatin», supervisor of qualification work: Inna OTRISHKO, PhD, assoc. prof.

approved by order of NUPh from «27th» of September_2024 № 237

2. Deadline for submission of qualification work by the applicant for higher education: May 2025

3. Outgoing data for qualification work: chronic coronary heart disease, rosuvastatin, efficacy and safety of therapy, medication adherence, Moroccan patients.

4. Contents of the settlement and explanatory note (list of questions that need to be developed):
To study the basic information about chronic coronary heart disease; to study the impact of adherence on quality of Moroccan chronic coronary heart disease patient's life; to study approaches to modern therapy of chronic coronary heart disease; to analyze the opinions and beliefs of pharmacy visitors with chronic coronary heart disease concerning efficacy and safety of medication management; to develop practical recommendations for physicians, pharmacists and patients about alternative ways to improve treatment adherences in Moroccan chronic coronary heart disease patients using rosuvastatin.

5. List of graphic material (with exact indication of the required drawings):
tables – 10, figures – 5.

6. Consultants of chapters of qualification work

Chapters	Name, SURNAME, position of consultant	Signature, date	
		assignment was issued	assignment was received
1.	Inna OTRISHKO, associate professor of higher education institution of pharmacology and clinical pharmacy department	30.09.2024	30.09.2024
2.	Inna OTRISHKO, associate professor of higher education institution of pharmacology and clinical pharmacy department	30.09.2024	30.09.2024
3.	Inna OTRISHKO, associate professor of higher education institution of pharmacology and clinical pharmacy department	30.09.2024	30.09.2024

7. Date of issue of the assignment: «30» September 2024

CALENDAR PLAN

№ з/п	Name of stages of qualification work	Deadline for the stages of qualification work	Notes
1.	Conducting a literature review on the issues of the work.	September-October 2024	**done**
2.	Conducting a survey of pharmacy visitors.	November-December 2024	**done**
3.	Experimental data processing.	January-February 2025	**done**
4.	Writing the qualification work.	Mach-April 2025	**done**
5.	Registration of the work and accompanying documents and submission to the Examination Committee of the NUPh.	May 2025	**done**

An applicant of higher education _____ Omar ELKADIRI

Supervisor of qualification work _____ Inna OTRISHKO

ВИТЯГ З НАКАЗУ № 237

По Національному фармацевтичному університету

від 27 вересня 2024 року

Затвердити теми кваліфікаційних робіт здобувачам вищої освіти 5-го курсу Фм20(4,10д) 2024-2025 навчального року, освітньо-професійної програми – Фармація, другого (магістерського) рівня вищої освіти, спеціальності 226 – Фармація, промислова фармація, галузь знань 22 Охорона здоров'я, денна форма здобуття освіти (термін навчання 4 роки 10 місяців), які навчаються за контрактом (мова навчання англійська та українська) згідно з додатком № 1.

Прізвище, ім'я здобувача вищої освіти	Тема кваліфікаційної роботи		Посада, прізвище та ініціали керівника	Рецензент кваліфікаційної роботи
по кафедрі фармакології та клінічної фармації				
Елькадірі Омар	Оцінка рівня прихильності до лікування марокканських пацієнтів з хронічною ішемічною хворобою серця при застосуванні препаратів розувастатину у складі комбінованої терапії	Evaluation of medication adherence among chronic coronary heart disease Moroccan patients using combination therapy with rosuvastatin	доцент Отрішко І.А.	професор Бутко Я.О.

Національний фармацевтичний університет
Факультет з підготовки іноземних громадян

Ректор

Вірно. Секретар

ФА2.8-03-317

ВИСНОВОК

експертної комісії про проведену експертизу
щодо академічного плагіату у кваліфікаційній роботі

здобувача вищої освіти

«04» травня 2025 р. № 331110414

Проаналізувавши кваліфікаційну роботу здобувача вищої освіти Елькадірі Омар, групи Фм20(4,10д) англ-04, спеціальності 226 Фармація, промислова фармація, освітньої програми «Фармація» навчання на тему: «Оцінка рівня прихильності до лікування марокканських пацієнтів з хронічною ішемічною хворобою серця при застосуванні препаратів розувастатину у складі комбінованої терапії / Evaluation of medication adherence among chronic coronary heart disease Moroccan patients using combination therapy with rosuvastatin», експертна комісія дійшла висновку, що робота, представлена до Екзаменаційної комісії для захисту, виконана самостійно і не містить елементів академічного плагіату (компіляції).

Голова комісії,
проректор ЗВО з НПР,
професор **Інна ВЛАДИМИРОВА**

Ф А 2.2.1-32-353

REVIEW

of scientific supervisor for the qualification work of the master's level of higher education of the specialty 226 Pharmacy, industrial pharmacy

Omar ELKADIRI

on the topic: «Evaluation of medication adherence among chronic coronary heart disease Moroccan patients using combination therapy with rosuvastatin»

Relevance of the topic. Coronary heart disease is a dynamic process of atherosclerotic plaque accumulation and functional changes in the coronary circulation, which can be reversed by lifestyle modification, pharmacological therapy and revascularization, leading to stabilization or regression of the disease.

Practical value of conclusions, recommendations and their validity. The research conducted in this work is the basis for further clinical and pharmaceutical studies, development and implementation of principles for optimizing the use of rosuvastatin. The implementation of these principles and provisions in practical medicine and pharmacy will help to increase the effectiveness and safety of chronic coronary heart disease therapy.

Assessment of work. The work is performed at a sufficient scientific and methodological level. In terms of relevance, scientific novelty and practical significance, it fully meets the requirements for qualification works.

General conclusion and recommendations on admission to defend. The work is performed in full, designed in accordance with the current requirements for the qualification works at the National University of Pharmacy and can be recommended for submission to the EC for further defense.

Scientific supervisor _____ Inna OTRISHKO

«09» May 2025

Ф А 2.2.1-32-356

REVIEW

for qualification work of the master's level of higher education, specialty 226 Pharmacy, industrial pharmacy

Omar ELKADIRI

on the topic: «Evaluation of medication adherence among chronic coronary heart disease Moroccan patients using combination therapy with rosuvastatin»

Relevance of the topic. Coronary heart disease (CHD) occurs as a result of absolute or relative impairment of myocardial blood supply due to coronary artery demage. A constant lack of blood supply to a particular area of the heart causes the development of chronic CHD, which can lead to sudden arrhythmia, coronary artery occlusion, myocardial infarction, and even death.

Theoretical level of work. The literature review conducted on the subject of the study illustrates the state of pharmaceutical care of patients today and outlines the prospects for research in this area.

Author's suggestions on the research topic. The provisions of the author of the work on pharmaceutical care are of practical importance for the modern health care system.

Practical value of conclusions, recommendations and their validity. According to the results of research, approaches to the rational use of rosuvastatin have been developed. The author discusses the main approaches to increase the medication adherence in case of chronic coronary heart disease therapy. Practical recommendations for all healthcare providers are proposed.

Disadvantages of work. Single grammatical and spelling errors do not affect the overall positive assessment of the work.

General conclusion and assessment of the work. The work meets the requirements for qualification work in NUPh and can be recommended for defense.

Reviewer _____ prof. Yaroslava BUTKO

«14» May 2025

Ф А2.2.1-38-287

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ
ВИТЯГ З ПРОТОКОЛУ № 19
засідання кафедри фармакології та клінічної фармації

15 травня 2025 р. м. Харків

Голова: завідувач кафедри, доктор мед. наук, професор Штриголь С. Ю.
Секретар: кандидат фарм. наук, доцент Вєтрова К. В.

ПРИСУТНІ: зав. каф., проф. Штриголь С.Ю., проф. Деримедвідь Л.В., доц. Бєлік Г.В., доц. Вєтрова К.В., доц. Жаботинська Н.В., доц. Кононенко А. В., доц. Матвійчук А.В., доц. Отрішко І.А., доц. Очкур О.В., доц. Рябова О.О., доц. Савохіна М.В., доц. Степанова С. І., доц. Таран А.В., ас. Верховодова Ю.В., ас. Підгайна В.В. та здобувачі вищої освіти.

ПОРЯДОК ДЕННИЙ:
1.Розгляд кваліфікаційних робіт здобувачів вищої освіти для подання робіт до Екзаменаційної комісії.

СЛУХАЛИ:
1.Здобувача вищої освіти Елькадірі Омара зі звітом про проведену наукову діяльність за темою кваліфікаційної роботи: «Оцінка рівня прихильності до лікування марокканських пацієнтів з хронічною ішемічною хворобою серця при застосуванні препаратів розувастатину у складі комбінованої терапії» («Evaluation of medication adherence among chronic coronary heart disease Moroccan patients using combination therapy with rosuvastatin»).

УХВАЛИЛИ:
1. Кваліфікаційну роботу розглянуто. Здобувач вищої освіти Елькадірі Омар допускається до захисту даної кваліфікаційної роботи в Екзаменаційній комісії.

Голова
Завідувач кафедри, проф. Штриголь С. Ю.

Секретар, доц. Вєтрова К. В.

Ф А2.2.1-32-042

НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ПОДАННЯ
ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ
ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ

Направляється здобувач вищої освіти Омар ЕЛЬКАДІРІ до захисту кваліфікаційної роботи
за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньо-професійною програмою Фармація
на тему: «Оцінка рівня прихильності до лікування марокканських пацієнтів з хронічною ішемічною хворобою серця при застосуванні препаратів розувастатину у складі комбінованої терапії» / «Evaluation of medication adherence among chronic coronary heart disease Moroccan patients using combination therapy with rosuvastatin».

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ / Микола ГОЛІК /

Висновок керівника кваліфікаційної роботи

Здобувач вищої освіти Омар ЕЛЬКАДІРІ виконав весь необхідний обсяг робіт. Кваліфікаційна робота може бути рекомендована до подачі в ЕК НФаУ для подальшого її захисту.

Керівник кваліфікаційної роботи

_____ Інна ОТРІШКО

«09» травня 2025 року

Висновок кафедри про кваліфікаційну роботу

Кваліфікаційну роботу розглянуто. Здобувач вищої освіти Омар ЕЛЬКАДІРІ допускається до захисту даної кваліфікаційної роботи в Екзаменаційній комісії.

Завідувач кафедри
фармакології та клінічної фармації Сергій ШТРИГОЛЬ

«15» травня 2025 року

Qualification work was defended
of Examination commission on
«___» June 2025
with the grade _____

Head of the State Examination commission,
DPharmSc, Professor
_____ / Volodymyr YAKOVENKO /