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Inclisiran in Patients With Acute Ischemic Stroke: First Data

Aim	To evaluate the effect of inclisiran therapy on parameters of lipid metabolism in hospitalized patients with acute ischemic stroke.
Material and methods	A prospective, observational, non-randomized study was performed. The study included 12 patients with acute ischemic stroke prescribed with a combination lipid-lowering therapy with inclisiran (284 mg as a single dose). At 15 days after the start of therapy, changes in blood lipid composition were assessed. For quantitative variables, median, maximum and minimum values were determined. The significance of differences between related samples in quantitative variables was assessed using the Mann–Whitney test.
Results	Before the start of combination lipid-lowering therapy, total cholesterol (TC) was 7.33 mmol/l and low-density lipoprotein C (LDL–C) was 5.23 mmol/l. At 15 days after the start of inclisiran therapy, TC significantly decreased by 52.1% and LDL–C decreased by 71.1%. The proportion of patients who reached the LDL–C goal was 66.7%. There were no adverse events considered by the investigators to be related with the therapy.
Conclusion	The strategy of early administration of inclisiran (or its combination with a statin) in patients with ischemic stroke allows safe achievement of a significant reduction in LDL–C already in 15 days after the start of therapy.

Keywords	Cardiovascular diseases; cardiovascular complications; stroke; ischemic stroke; dyslipidemia; lipid-lowering therapy; inclisiran; compliance with treatment
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Introduction

Cardiovascular diseases (CVDs) rank first among causes of death in older patients [1]. The COVID-19 pandemic did not change the situation and, on the contrary, emphasized the importance of correcting risk factors of adverse cardiovascular events in various clinical situations [2, 3]. In 2018, in the Russian Federation, the cerebrovascular mortality was 31% of the circulatory disease mortality [4], which corresponds to worldwide data, according to which stroke ranks second (after coronary artery disease) among the causes of death of the population [5]. Persistently high mortality in the acute period (15%), despite continuously improving system of care for patients with cerebral accidents [6], and the high incidence of disability underscore the relevance of the problem of ischemic stroke (IS). Stroke is the leading cause of disability in the Russian Federation (3.2 cases per 1,000 people) [4]. As well as the primary prevention of IS, reducing the risk of recurrent IS seems to be an equally important task, given the available epidemiological data – the one-year risk of developing recurrent IS is 7–20%, recurrent acute cerebrovascular accident is observed in 16–35% of patients within 5 years [7, 8]. The importance of these figures is emphasized by a significantly higher risk of death after recurrent IS (up to 70% of patients within 10 years) [9].

Dyslipidemia is one of the most well-studied modifiable cardiovascular risk factors [10]. This statement is also totally relevant for IS [11]. For example, elevated low-density lipoprotein (LDL) cholesterol is associated not only with atherosclerosis of the brachiocephalic arteries, transient ischemic attack (TIA) and IS, but is also a risk factor for carotid restenosis after surgical treatment, and is also associated with a worse functional outcome and an unfavorable long-term prognosis for life after a cerebral accident [12]. LDL cholesterol is considered as the main target for lipid-lowering therapy (LLT) to reduce the risk of IS and recurrent cerebral accidents [13]. A decrease in the level of LDL cholesterol by 1 mmol/L reduces the risk

of ischemic stroke by 12% [14]. According to the consensus of experts, the target value of LDL cholesterol for patients at very high risk, including those who have history of IS, should be considered less than 1.4 mmol/L [15]. Even though dyslipidemia may be corrected with medication, achieving the target values is a challenge in real-world clinical practice. This fact allowed the expert community to change the modern concept of achieving target levels of LDL cholesterol using "high-intensity statin therapy" to "high-intensity lipid-lowering therapy" [16]. The updated approach implies the early administration of combination therapy in patients with LDL cholesterol > 5.0 mmol/L including with the use of monoclonal antibodies and a new class of drugs – small interfering RNA, the sole representative of which is inclisiran. This provision is reflected in the new clinical guideline of the Ministry of Health of the Russian Federation "Lipid Metabolism Disorders" [15].

The mechanism of RNA interference behind the inclisiran effect is associated with the ability to stop proprotein convertase subtilisin/kexin type 9 (PCSK9) synthesis in hepatocytes in being prepared for the assembly of this protein, which essentially eliminated the underlying cause of hypercholesterolemia. After penetrating a hepatocyte, inclisiran enters the endosomes and forms the depot. It is slowly released from the endosomes into the cytoplasm, where its guide strand binds to the RNA-inducible gene silencing complex [17]. Its activation leads to specific binding and destruction of mRNA to PCSK9, which serves as a matrix for the reproduction of this protein. Inhibition of PCSK9 synthesis provides high activity of LDL cholesterol receptors on the surface of hepatocytes, which allows them to be captured from blood plasma, thus the concentration of LDL cholesterol is reduced.

According to the draft clinical guideline Ischemic Stroke and Transient Ischemic Attack in Adults (2023), inclisiran can be administered as part of a combination LLT in patients with history of IS or TIA [18]. In this regard, applying the results of randomized controlled trials (RCTs) showing the high efficacy of inclisiran [19] in the real-world clinical practice is an important task for the implementation of modern approaches to the correction of dyslipidemia, particularly in patients with IS [20].

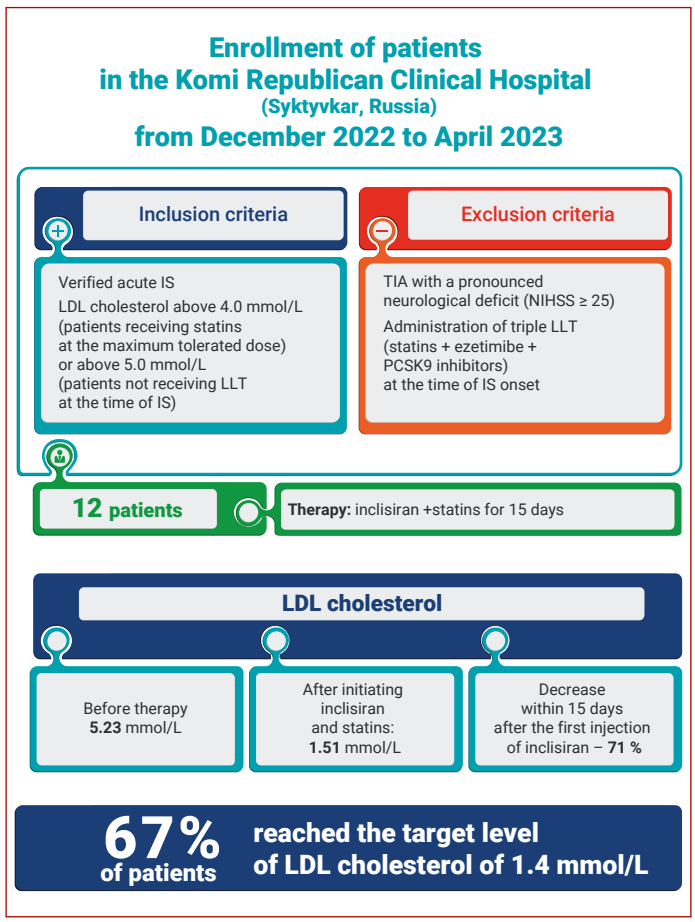
Objective

Evaluate the short-term effect of combination LLT with inclisiran and its safety in the group of patients with ischemic stroke initiated within three days after onset.

Material and Methods

Prospective observational non-randomized study was conducted in the Komi Republican Clinical Hospital (Syktyvkar, Russia) from December 2022 to April 2023. The inclusion criteria comprised documented acute IS, LDL cholesterol >4.0 mmol/L (patients taking statins at the maximum tolerated dose) or more than 5.0 mmol/L (patients not receiving LLT at the time of IS). The exclusion criteria were TIA patients with a pronounced neurological deficit (NIHSS ≥ 25) who took triple LLT (statins + ezetimibe + PCSK9 inhibitors) at the time of onset of IS. Lipid profile was examined in all patients within the first hours after the admission to the ICU. All patients were considered as having hyperlipidemia (hyperlipoproteinemia – HLP) type IIa. Inclisiran (Sibrava, Novartis, Switzerland) was administered at a single dose of 284 mg (1.5 ml) subcutaneously to the abdomen to 12 patients who met these criteria, in addition to prescribing high-intensity statin therapy (atorvastatin 40 mg once a day) or continuing previously used such therapy. All patients included in the study were considered as having HLP type IIa. Clinical relevance of the drug administration was confirmed by the medical board. All patients signed informed consent. In addition to LLT, patients received background therapy and antithrombotic therapy in accordance with the pathogenetic subtype of IS and the time after onset of cerebral accident. Sex, age, pathogenetic variant

Central illustration



IS, ischemic stroke; TIA, transient ischemic attack; LLT, lipid-lowering therapy

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Table 1. Characteristics of patients examined

Parameter	Value
Sex, n (%)	
• Male	5 (41.6)
• Female	7 (58.3)
Age, years, Me (Min-Max)	62.3 (49–75)
Pathogenetic subtype of ischemic stroke (according to the SSS-TOAST* classification), n (%)	
Atherothrombotic	3 (25)
Lacunar	2 (16.6)
Cardioembolic	2 (16.6)
Other specified origin	0
Unspecified origin	5 (41.6)
Unknown cause of IS	4 (33.3)
Two or more probable causes	1 (16.6)
Severity of neurological deficit (NIHSS) at admission, Me (Min-Max)	7.2 (1–17)
Risk factors for cardiovascular diseases and the presence of a concomitant condition, n (%)	
History of IS	2 (16.6)
Smoking	2 (16.6)
Body mass index ≥ 30 kg/m^2	3 (25)
Arterial hypertension	10 (83.3)
Coronary artery disease	5 (41.6)
Diabetes mellitus type 2	3 (25)
Lipid-lowering therapy before ischemic stroke	2 (16.6)
Time to the administration of inclisiran after the onset of ischemic stroke, h, Me (Min-Max)	44.2 (24–120)

* Adapted from [21].

of IS, and severity of neurological deficit, administration of LLT at the time of cerebral accident, and the presence of comorbidity in patients included in the study are presented in Table 1. The mean time to initiation of therapy after onset of IS was 44.2 hours. The risk of developing adverse cardiovascular events was assessed as very high in all patients, the study did not include patients at extreme risk (following the criteria specified in the National Clinical Guidelines [15]). We evaluated the parameters of the lipid profile (total cholesterol (TC), LDL cholesterol, HDL cholesterol, TG) before and 15 days after initiating inclisiran therapy.

The statistical analysis of data was conducted in SPSS 23.0. Given the size of the sample (n = 12), its distribution was not assessed. The median, maximum and minimum values were determined for quantitative variables. The Mann-Whitney test was used to evaluate the significance of differences in quantitative variables between related samples. The study was conducted in accordance with the Declaration of Helsinki (adopted in June 1964, revised in October 2013), and approved by the local ethics committee. Characteristics of patients examined are provided in Table 1.

Results

Fifteen days after starting LLT with inclisiran, TC was 3.51 mmol/L, which corresponded to statistically significant mean decrease in this parameter by 52.1%. The greatest changes were observed for LDL cholesterol, the absolute decrease of which was 1.51 mmol/L, which corresponded to a 71.1% decrease (Table 2). After 15 days, 8 (66.7%) patients reached the target level of 1.4 mmol/L ($p<0.05$). There were no serious adverse events that were treatment-related according to the investigators.

Discussion

Real-world clinical data on the use of inclisiran in separate national centers for the treatment of atherosclerosis [22, 23] and in certain specific groups of patients [24] are actively submitted for analysis to the scientific community. Our study demonstrates the possibility of initiating high-intensity LLT with inclisiran in patients with acute IS. The findings show the possibility of not only a significant decrease in the levels of LDL cholesterol at discharge from the hospital (–71.1% decrease in LDL cholesterol) and the possibility of achieving the target values of LDL cholesterol 14 days after onset of IS. Moreover, given the fact that inclisiran realizes only 80% of its hypolipidemic effect by day 14 [25], it is assumed that the percentage of patients who achieve the target value of LDL cholesterol will increase in case of subsequent dynamic follow-up without correction of the initiated therapy. It is important to point out that our findings (estimation of the effect in 15 days) do not cancel

Table 2. Changes in blood lipid profile during the combination lipid-lowering therapy with inclisiran

Indicator, mmol/L, Me (Min–Max)	Parameter of blood lipid profile		
	Before lipid-lowering therapy with inclisiran	15 days after the beginning of lipid-lowering therapy with inclisiran	Change, %
TC	7.33 (5.81–9.21)	3.51 (1.81–5.29)	-52.1*
LDL cholesterol	5.23 (4.34–6.99)	1.51 (0.73–3.11)	-71.1*
HDL cholesterol	1.13 (0.81–1.22)	1.24 (0.90–1.36)	+9.7
TG	1.71 (1.28–2.89)	1.57 (1.18–2.42)	-8.7

* Intergroup differences are significant ($p < 0.05$, Mann-Whitney test).
TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides.

the need to further assess the effect of combination LLT in accordance with the terms specified in the current clinical guidelines.

The presented experience of using inclisiran in patients with IS provides an opportunity to discuss several relevant practical aspects of using LLT in cerebral accidents.

Compliance

Compliance with long-term therapy for secondary prevention may be significantly lower in patients with IS than in patients with history of MI, the percentage of compliant patients may be even lower (not more than 59%) in the case of LLT [26]. At the same time, missing daily doses due to forgetfulness is one of the patient-associated risk factors of poor compliance [27]. Given the fact that drugs with a more convenient mode of administration (for example, injections once every 3 months) changed the compliance of patients with certain neurological diseases [28], a similar effect should be expected for inclisiran in patients with history of IS. This assumption is based on the available results of studies of therapeutic interventions for the secondary prevention of cerebral accidents that show a greater clinical benefit of using certain drugs in patients highly adherent to treatment [29, 30].

Swallowing dysfunction and mobility restrictions after IS are the factors that are associated with the complications and a higher risk of mortality in the early and late recovery periods after cerebral accidents [31, 32] and the reasons for refusal or low adherence to long-term therapy for secondary prevention of IS [33]. From this point of view, treatment with inclisiran initiated in the acute period of IS has such advantages as a convenient regimen and mode of administration (subcutaneous injection once every 6 months), can increase the chance of long-term compliance with the administered LLT during medical rehabilitation and subsequent outpatient management, including in patients with dysphagia and severe paresis.

Combination LLT after IS and time of initiation

The DA VINCI study [34] showed that after reducing the target values of LDL cholesterol, the percentage of patients who do not achieve the established parameter expectedly increased. According to the SANTORINI study, the target LDL cholesterol levels indicated in the 2019 ESC guideline [35] are achieved by 20.1% of patients at high and very high risk, and combination LLT is used in not more than 24.0% of cases [36]. The paradigm shift from "high-intensity statin therapy" to "high-intensity lipid-lowering therapy" in terms of early administration of combination LLT as initial therapy is considered as one of the factors that will optimize treatment of patients with dyslipidemia in real-world clinical practice [16].

In our study, we used inclisiran as a part of high-intensity LLT, during which the target levels of LDL cholesterol were achieved in 8 (66.7%) patients during hospital stay. Time of initiating LLT after IS remains a subject of discussion from the point of view of achieving clinical benefits (for example, via the pleiotropic effects of statins prescribed in the very first days after cerebral accident) [37]. Perhaps the initiation of therapy with small interfering RNA after IS in hospital may be considered as an important tool for correcting dyslipidemia in real-world clinical practice from the point of view of the initiating LLT at the best possible power and reducing the risk of organizational and clinical errors when choosing LLT at subsequent stages of therapy. This approach is used by the European Project Task Force with the ambitious goal of achieving the target values in 76% of patients after acute coronary syndrome within the next 3 months (ACS EuroPath III) after onset of the event, while the Project Task Force notes that the lack of adequately selected LLT at discharge from hospital is the main problem in achieving this goal [38].

Given the fact that recurrent stroke develops mainly in the first month after the first cerebral accident, early intensive therapy, including the best-possible and lipid-lowering therapy, is a feasible treatment strategy [39]. Initiating inclisiran after IS should be a driver of the best-possible LLT at subsequent stages of the patient management (including outpatient), because it is the long-term and stable maintenance of the achieved decrease in the levels of LDL cholesterol that allows minimizing the risk of developing recurrent IS [40]. Apparently, the administration of inclisiran will not only achieve the target levels of LDL cholesterol but also make it possible to prevent adverse events, such as cerebral accidents, which can be beneficial from the point of view of reducing the financial burden on the health care system [41]. There were no adverse events during inclisiran therapy, including those that led to prolongation of hospital treatment, development of life-threatening conditions, or aggravation of the recovery period. No patients developed hemorrhagic transformation of cerebral infarction.

Decreased LDL cholesterol

In our study, LDL cholesterol decreased to 0.7 mmol/L in three patients. Safety of low LDL cholesterol from the point of view of the risk of hemorrhagic stroke is being discussed, and the very concept of very low LDL cholesterol levels has changed over time. Meta-analysis Cholesterol Treatment Trialists Collaboration showed the safety of decreasing the levels of LDL cholesterol below 1.8 mmol/L [14], and currently, this level is considered acceptable only for patients at high risk of adverse cardiovascular events [42]. Attention should be

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ЗНАЮ. ВИЖУ. СНИЖАЮ?

~75% пациентов с АССЗ не достигают целевого уровня ХС ЛНП на текущей* терапии[1]

Снижение уровня ХС ЛНП на 1 ммоль/л снижает риск сердечно-сосудистых катастроф** на 22%[2]

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ХС ЛНП – холестерин липопротеидов низкой плотности.
АССЗ – атеросклеротические сердечно-сосудистые заболевания. * липидснижающей, ** инфаркта миокарда и ишемического инсульта

1. Cannon CP, et al. JAMA Cardiol. 2017;2(9):959-966.
2. Baigent C, et al. Lancet. 2010;376(9753):1670-1681.

Гипотетический пациент

paid now to the safety of LDL cholesterol levels less than 1.0 mmol/L. The accumulated data suggest no increased risk of some complications when the target values are achieved. No increased risk of intracranial hemorrhage during the use of PCSK9 inhibitors, including in the group of patients with LDL cholesterol <0.5 mmol/L, was observed in RCTs [43, 44] and post-hoc RCT analysis [45]. An analysis of the outcomes of 2,669 patients who achieved LDL cholesterol levels <0.5 mmol/L in the FOURIER study showed no increased risk of hemorrhagic stroke, neurocognitive events, non-cardiac death, and other diseases in this group of patients. The absence of danger "signals" of the increased risk of intracranial hemorrhage and other serious complications in the analysis of the 4 year follow-up of patients of a series of double-blind randomized placebo-controlled studies ORION-1 and ORION-3 shows the long-term safety of maintaining low LDL cholesterol levels and administering inclisiran [46]. Moreover, a targeted safety analysis of inclisiran in patients with underlying cerebrovascular diseases, who were included in the ORION-9, ORION-10, and ORION-11 studies, also did not reveal any additional danger signals in this group of patients [47]. Practically speaking, lowering LDL cholesterol levels to less than 1.0 mmol/l does not require dose adjustment and it can be advised to maintain the achieved treatment result in the long term without modifying the conducted LLT.

Effects on lipoprotein (a)

We did not determine the levels of lipoprotein (a) (Lp (a)) in our study. However, in the absence of drugs targeted at reducing the Lp (a) levels, a 19–25% decrease in this parameter during inclisiran therapy can surely be its advantage [48]. Given the available data on the causal relationship of increased levels of Lp (a) and the risk of IS [49], using of inclisiran within LLT may cause an additional reduction in the risk of recurrent adverse cardiovascular events in patients with increased levels of Lp (a).

The limitations of the study were a single-center uncontrolled design, an unblinded patient observation protocol, and a small sample size. These limitations did not affect the results and conclusions of our study given the objective nature of laboratory control of LDL cholesterol in high lipid-lowering efficacy of inclisiran, which allows obtaining statistically significant results in a small sample. Despite the fact that there was a clear decrease in the levels of LDL cholesterol in early administration of inclisiran in the high-risk population of interest, our study was not designed to assess clinical outcomes, which requires a sample and a statistical plan with adequate power. We also did not assess the effect of some background and concomitant treatments for the therapy of IS, which could potentially affect the lipid profile.

Conclusion

It can be assumed that the use of inclisiran can change the current practice of LLT after IS [50]. The use of small interfering RNA can objectively improve the control of dyslipidemia in patients after IS in real-world clinical practice as the achievement of the target levels of LDL cholesterol that is considered the main treatment target, and there is a clear problem of poor compliance and suboptimal continuity of long-term LLT after cerebral accidents [51]. The first experience of using inclisiran in patients with acute IS showed the possibility of early initiation of the administration of this drug in hospital and achievement of the target values of LDL cholesterol at discharge. In summary, we can assume that one of the most effective and safe therapeutic strategies to reduce the risk of recurrent cardiovascular complications in a number of patients with IS is the initiation of combination LLT with small interfering RNA in the acute period of cerebral accident.

No conflict of interest is reported.

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REFERENCES

1. Boytsov S.A., Shalnova S.A., Deev A.D. Cardiovascular mortality in the Russian Federation and possible mechanisms of its changes. S.S. Korsakov Journal of Neurology and Psychiatry. 2018;118(8):98–103. [Rusian: Бойцов С.А., Шальнова С.А., Деев А.Д. Смертность от сердечно-сосудистых заболеваний в Российской Федерации и возможные механизмы ее изменения. Журнал неврологии и психиатрии им. С.С. Корсакова. 2018;118(8):98-103]. DOI: 10.17116/jnevro201811808198
2. Quinn KL, Lam GY, Walsh JF, Bhéreur A, Brown AD, Chow CW et al. Cardiovascular Considerations in the Management of People With Suspected Long COVID. Canadian Journal of Cardiology. 2023;39(6):741–53. DOI: 10.1016/j.cjca.2023.04.003
3. Chilazi M, Duffy EY, Thakkar A, Michos ED. COVID and Cardiovascular Disease: What We Know in 2021. Current Atherosclerosis Reports. 2021;23(7):37. DOI: 10.1007/s11883-021-00935-2
4. Federal State Statistics Service. Health in Russia. 2019. Statistical book. -M.: Rosstat;2019. - 170p. [Russian: Федеральная служба государственной статистики. Здравоохранение в России. 2019. Статистический сборник. - М.: Росстат, 2019. - 170с. Доступно на: https://www.gks.ru/storage/mediabank/Zdravoohran-2019.pdf]. ISBN 978-5-89476-470-2
5. Johnson CO, Nguyen M, Roth GA, Nichols E, Alam T, Abate D et al. Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Neurology. 2019;18(5):439–58. DOI: 10.1016/S1474-4422(19)30034-1
6. Gattringer T, Posekany A, Niederkorn K, Knoflach M, Poltrum B, Mutzenbach S et al. Predicting Early Mortality of Acute Ischemic Stroke: Score-Based Approach. Stroke. 2019;50(2):349–56. DOI: 10.1161/STROKEAHA.118.022863

ISSN 0022-9040. Kardiologiia. 2023;63(10). DOI: 10.18087/cardio.2023.10.n2560

7. Boulanger M, Béjot Y, Rothwell PM, Touzé E. Long-Term Risk of Myocardial Infarction Compared to Recurrent Stroke After Transient Ischemic Attack and Ischemic Stroke: Systematic Review and Meta-Analysis. Journal of the American Heart Association. 2018;7(2):e007267. DOI: 10.1161/JAHA.117.007267
8. Mohan KM, Wolfe CDA, Rudd AG, Heuschmann PU, Kolominsky-Rabas PL, Grieve AP. Risk and cumulative risk of stroke recurrence: a systematic review and meta-analysis. Stroke. 2011;42(5):1489–94. DOI: 10.1161/STROKEAHA.110.602615
9. Skajaa N, Adelborg K, Horváth-Puhó E, Rothman KJ, Henderson VW, Thygesen LC et al. Risks of Stroke Recurrence and Mortality After First and Recurrent Strokes in Denmark: A Nationwide Registry Study. Neurology. 2021; [Online ahead of print]. DOI: 10.1212/WNL.0000000000013118
10. Boytsov S.A., Drapkina O.M., Shlyakhto E.V., Konradi A.O., Balanova Yu.A., Zhernakova Yu.V. et al. Epidemiology of Cardiovascular Diseases and their Risk Factors in Regions of Russian Federation (ESSE-RF) study. Ten years later. Cardiovascular Therapy and Prevention. 2021;20(5):143–52. [Russian: Бойцов С.А., Драпкина О.М., Шляхто Е.В., Конради А.О., Баланова Ю.А., Жернакова Ю.В. и др. Исследование ЭССЕ-РФ (Эпидемиология сердечно-сосудистых заболеваний и их факторов риска в регионах Российской Федерации). Десять лет спустя. Кардиоваскулярная терапия и профилактика. 2021;20(5):143-52]. DOI: 10.15829/1728-8800-2021-3007
11. Boehme AK, Esenwa C, Elkind MSV. Stroke Risk Factors, Genetics, and Prevention. Circulation Research. 2017;120(3):472–95. DOI: 10.1161/CIRCRESAHA.116.308398
12. Paraskevas KI, Veith FJ, Eckstein H-H, Ricco J-B, Mikhailidis DP. Cholesterol, carotid artery disease and stroke: what the vascular specialist needs to know. Annals of Translational Medicine. 2020;8(19):1265. DOI: 10.21037/atm.2020.02.176
13. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D et al. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. Stroke. 2021;52(7):e364–467. DOI: 10.1161/STR.0000000000000375
14. Sabatine MS, Wiviott SD, Im K, Murphy SA, Giugliano RP. Efficacy and Safety of Further Lowering of Low-Density Lipoprotein Cholesterol in Patients Starting With Very Low Levels: A Meta-analysis. JAMA cardiology. 2018;3(9):823–8. DOI: 10.1001/jamacardio.2018.2258
15. Ezhov M.V., Kukharchuk V.V., Sergienko I.V., Alieva A.S., Antsiferov M.B., Ansheles A.A. et al. Disorders of lipid metabolism. Clinical Guidelines 2023. Russian Journal of Cardiology. 2023;28(5):250–97. [Russian: Ежов М.В., Кухарчук В.В., Сергиенко И.В., Алиева А.С., Анциферов М.Б., Аншелес А.А. и др. Нарушения липидного обмена. Клинические рекомендации 2023. Российский кардиологический журнал. 2023;28(5):250-97]. DOI: 10.15829/1560-4071-2023-5471
16. Ray KK, Reeskamp LF, Laufs U, Banach M, Mach F, Tokgözoğlu LS et al. Combination lipid-lowering therapy as first-line strategy in very high-risk patients. European Heart Journal. 2022;43(8):830–3. DOI: 10.1093/eurheartj/ehab718
17. Cupido AJ, Kastelein JJP. Inclisiran for the treatment of hypercholesterolaemia: implications and unanswered questions from the ORION trials. Cardiovascular Research. 2020;116(11):e136–9. DOI: 10.1093/cvr/cvaa212
18. Ischemic stroke and transient ischemic attack in adults. Clinical recommendations. 2022. Av. at: https://evidence-neurology.ru/content/downloadfiles/13/kr-po-ii-i-tia_2022_finalnii-v_ru_1650370148.pdf. [Russian: Ишемический инсульт и транзиторная ишемическая атака у взрослых. Клинические рекомендации. 2022. Доступно на: https://evidence-neurology.ru/content/downloadfiles/13/kr-po-ii-i-tia_2022_finalnii-v_ru_1650370148.pdf]
19. Ray KK, Wright RS, Kallend D, Koenig W, Leiter LA, Raal FJ et al. Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. New England Journal of Medicine. 2020;382(16):1507–19. DOI: 10.1056/NEJMoa1912387
20. Boytsov S.A., Piradov M.A., Tanashyan M.M., Voznyuk I.A., Yezhov M.V., Oshchepkova E.V. et al. Topical issues of adequate control of dyslipidemia in the prevention of acute and recurrent cerebral circulatory disorders of ischemic type. S.S. Korsakov Journal of Neurology and Psychiatry. 2022;122(5):7–10. [Russian: Бойцов С.А., Пирадов М.А., Танашян М.М., Вознюк И.А., Ежов М.В., Ощепкова Е.В. и др. Актуальные вопросы адекватного контроля дислипидемий в профилактике острых и повторных нарушений мозгового кровообращения по ишемическому типу. Журнал неврологии и психиатрии им. С.С. Корсакова. 2022;122(5):7-10]. DOI: 10.17116/jnevro20221220517
21. Ay H, Benner T, Murat Arsava E, Furie KL, Singhal AB, Jensen MB et al. A Computerized Algorithm for Etiologic Classification of Ischemic Stroke: The Causative Classification of Stroke System. Stroke. 2007;38(11):2979–84. DOI: 10.1161/STROKEAHA.107.490896
22. Luo Z, Huang Z, Sun F, Guo F, Wang Y, Kao S et al. The clinical effects of inclisiran, a first-in-class LDL-C lowering siRNA therapy, on the LDL-C levels in Chinese patients with hypercholesterolemia. Journal of Clinical Lipidology. 2023;17(3):392–400. DOI: 10.1016/j.jacl.2023.04.010
23. Medvedeva E.A., Grigorenko E.A., Mitkovskaya N.P. Innovative lipid-lowering therapy: experience of inclisiran use in the Republic of Belarus. Russian Journal of Cardiology. 2023;28(4):53–61. [Russian: Медведева Е.А., Григоренко Е.А., Митьковская Н.П. Инновационная гиполипидемическая терапия: опыт применения инклисирана в Республике Беларусь. Российский кардиологический журнал. 2023;28(4):53-61]. DOI: 10.15829/1560-4071-2023-5417
24. Ueberdiek L, Jehn U, Pavenstädt H, Gebauer K, Reuter S. Novel Therapeutic Strategies for Dyslipidemia: First Report of Inclisiran Therapy in a Kidney Transplanted Patient. Transplant International. 2023;36:11104. DOI: 10.3389/ti.2023.11104
25. Ray KK, Landmesser U, Leiter LA, Kallend D, Dufour R, Karakas M et al. Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol. New England Journal of Medicine. 2017;376(15):1430–40. DOI: 10.1056/NEJMoa1615758
26. Shafqat S, Arif H, Aijaz B, Islam M, Aftab U, Kumar S. Drug compliance after stroke and myocardial infarction: A comparative study. Neurology India. 2007;55(2):130–5. DOI: 10.4103/0028-3886.32783
27. Rajahthurai SD, Farrukh MJ, Makmor-Bakry M, Tan HJ, Fatokun O, Mohd Saffian S et al. Use of Complementary and Alternative Medicine and Adherence to Medication Therapy Among Stroke Patients: A Meta-analysis and Systematic Review. Frontiers in Pharmacology. 2022;13:870641. DOI: 10.3389/fphar.2022.870641
28. Krasenbaum LJ, Pedarla VL, Thompson SF, Tangirala K, Cohen JM, Driessen MT. A real-world study of acute and preventive medication use, adherence, and persistence in patients prescribed fremanezumab in the United States. The Journal of Headache and Pain. 2022;23(1):54. DOI: 10.1186/s10194-022-01413-z
29. Spence JD, Viscoli CM, Inzucchi SE, Dearborn-Tomazos J, Ford GA, Gorman M et al. Pioglitazone Therapy in Patients With Stroke and Prediabetes: A Post Hoc Analysis of the IRIS Randomized Clinical Trial. JAMA Neurology. 2019;76(5):526–35. DOI: 10.1001/jamaneurol.2019.0079
30. Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M et al. Pioglitazone after Ischemic Stroke or Transient Ischemic Attack. New England Journal of Medicine. 2016;374(14):1321–31. DOI: 10.1056/NEJMoa1506930
31. Yang Y, Shi Y-Z, Zhang N, Wang S, Ungvari GS, Ng CH et al. The Disability Rate of 5-Year Post-Stroke and Its Correlation Factors: A National Survey in China. PLOS ONE. 2016;11(11):e0165341. DOI: 10.1371/journal.pone.0165341
32. Banda KJ, Chu H, Kang XL, Liu D, Pien L-C, Jen H-J et al. Prevalence of dysphagia and risk of pneumonia and mortality in acute stroke patients: a meta-analysis. BMC Geriatrics. 2022;22(1):420. DOI: 10.1186/s12877-022-02960-5
33. Al AlShaikh S, Quinn T, Dunn W, Walters M, Dawson J. Predictive factors of non-adherence to secondary preventative medication af-

ter stroke or transient ischaemic attack: A systematic review and meta-analyses. European Stroke Journal. 2016;1(2):65–75. DOI: 10.1177/2396987316647187
34. Ray KK, Molemans B, Schoonen WM, Giovas P, Bray S, Kiru G et al. EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care: the DA VINCI study. European Journal of Preventive Cardiology. 2021;28(11):1279–89. DOI: 10.1093/eurjpc/zwaa047
35. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. European Heart Journal. 2020;41(1):111–88. DOI: 10.1093/eurheartj/ehz455
36. Ray KK, Haq I, Bilitou A, Manu MC, Burden A, Aguiar C et al. Treatment gaps in the implementation of LDL cholesterol control among high- and very high-risk patients in Europe between 2020 and 2021: the multinational observational SANTORINI study. The Lancet Regional Health - Europe. 2023;29:100624. DOI: 10.1016/j.lanepe.2023.100624
37. Yanishevskiy S.N., Skiba Ya.B., Polushin A.Yu. Statins in patients with acute ischemic stroke: when we should start therapy? Arterial Hypertension. 2021;27(1):16–28. [Russian: Янишевский С.Н., Скиба Я.Б., Полушин А.Ю. Статины у пациента с ишемическим инсультом: как рано начинать терапию? Артериальная гипертензия. 2021;27(1):16-28]. DOI: 10.18705/1607-419X-2021-27-1-16-28
38. Catapano AL, De Caterina R, Jukema JW, Klempfner R, Landmesser U, Schiele F et al. Addressing current challenges in optimization of lipid management following an ACS event: Outcomes of the ACS EuroPath III initiative. Clinical Cardiology. 2023;46(4):407–15. DOI: 10.1002/clc.23988
39. Li S, Peng Y, Wang X, Qian Y, Xiang P, Wade SW et al. Cardiovascular events and death after myocardial infarction or ischemic stroke in an older Medicare population. Clinical Cardiology. 2019;42(3):391–9. DOI: 10.1002/clc.23160
40. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ. 2003;326(7404):1423. DOI: 10.1136/bmj.326.7404.1423
41. Ostwald DA, Schmitt M, Peristeris P, Gerritzen T, Durand A. The Societal Impact of Inclisiran in England: Evidence From a Population Health Approach. Value in Health. 2023;26(9):1353–62. DOI: 10.1016/j.jval.2023.05.002
42. What's new in clinical guideline Ministry of Health RF 'Disorders of lipid metabolism 2023'. Av. at: https://scardio.ru/content/activities/2023/11042023.pdf. [Russian: Что нового в клинических рекомендациях Минздрава РФ «Нарушения липидного обмена» 2023 г. Доступно на: https://scardio.ru/content/activities/2023/11042023.pdf]
43. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. New England Journal of Medicine. 2017;376(18):1713–22. DOI: 10.1056/NEJMoa1615664
44. Kiyosue A, Honarpour N, Kurtz C, Xue A, Wasserman SM, Hirayama A. A Phase 3 Study of Evolocumab (AMG 145) in Statin-Treated Japanese Patients at High Cardiovascular Risk. The American Journal of Cardiology. 2016;117(1):40–7. DOI: 10.1016/j.amjcard.2015.10.021
45. Ray KK, Ginsberg HN, Davidson MH, Pordy R, Bessac L, Minini P et al. Reductions in Atherogenic Lipids and Major Cardiovascular Events: A Pooled Analysis of 10 ODYSSEY Trials Comparing Alirocumab With Control. Circulation. 2016;134(24):1931–43. DOI: 10.1161/CIRCULATIONAHA.116.024604
46. Ray KK, Troquay RPT, Visseren FLJ, Leiter LA, Scott Wright R, Vikarunnessa S et al. Long-term efficacy and safety of inclisiran in patients with high cardiovascular risk and elevated LDL cholesterol (ORION-3): results from the 4-year open-label extension of the ORION-1 trial. The Lancet Diabetes & Endocrinology. 2023;11(2):109–19. DOI: 10.1016/S2213-8587(22)00353-9
47. Koenig W, Ray KK, Landmesser U, Leiter LA, Schwartz GG, Wright RS et al. Efficacy and safety of inclisiran in patients with cerebrovascular disease: ORION-9, ORION-10, and ORION-11. American Journal of Preventive Cardiology. 2023;14:100503. DOI: 10.1016/j.ajpc.2023.100503
48. Katsiki N, Vrablik M, Banach M, Gouni-Berthold I. Inclisiran, Low-Density Lipoprotein Cholesterol and Lipoprotein (a). Pharmaceuticals. 2023;16(4):577. DOI: 10.3390/ph16040577
49. Pan Y, Li H, Wang Y, Meng X, Wang Y. Causal Effect of Lp(a) [Lipoprotein(a)] Level on Ischemic Stroke and Alzheimer Disease: A Mendelian Randomization Study. Stroke. 2019;50(12):3532–9. DOI: 10.1161/STROKEAHA.119.026872
50. Nambi V, Agha A. Inclisiran: A Game Changer in a Changing Game? Journal of the American College of Cardiology. 2021;77(9):1194–6. DOI: 10.1016/j.jacc.2021.01.008
51. Tanashyan M.M., Shamalov N.A., Voznyuk I.A., Yanishevsky S.N., Vinogradov O.I., Khasanova D.R. et al. Control of dyslipidemia in the prevention of recurrent ischemic cerebrovascular accidents (expert opinion). Neurology, Neuropsychiatry, Psychosomatics. 2022;14(4):108–13. [Russian: Танашян М.М., Шамалов Н.А., Вознюк И.А., Янишевский С.Н., Виноградов О.И., Хасанова Д.Р. и др. Контроль дислипидемии в профилактике повторных ишемических нарушений мозгового кровообращения (заключение экспертов). Неврология, нейропсихиатрия, психосоматика. 2022;14(4):108-13]. DOI: 10.14412/2074-2711-2022-4-108-113

ISSN 0022-9040. Kardiologiia. 2023;63(10). DOI: 10.18087/cardio.2023.10.n2560