

Alekyan B.G., Karapetyan N.G., Chupin A.V.,
Zotikov A.E., Varava A. B., Knysh Yu.B., Sedgaryan M. A.
 Vishnevsky National Medical Research Center of Surgery, Moscow, Russia

LONG-TERM RESULTS OF THE TREATMENT OF PATIENTS WITH CHRONIC ISCHEMIA OF THE LOWER LIMBS IN COMBINATION WITH ISCHEMIC HEART DISEASE

<i>Aim</i>	To compare long-term outcomes of x-ray endovascular (percutaneous coronary intervention, PCI, and lower limb angioplasty with stent placement, LLA; group 1) and combination treatments (PCI and open LLA surgery; group 2) in patients with chronic lower limb ischemia (CLLI) associated with ischemic heart disease (IHD).
<i>Material and methods</i>	This retrospective study has been conducted in the Vishnevsky National Medical Research Center of Surgery since 2019. The study includes 92 patients with stage 2B CLLI associated with IHD who were managed from January 1, 2017 through December 31, 2020. Long-term outcomes were evaluated in 76 (82.6%) patients. The endpoint was severe cardiovascular complications (CVC), including death, myocardial infarction, and acute cerebrovascular disease (ACVD).
<i>Results</i>	In group 1 during the long-term period, 1 (2.7%) fatal outcome due to pneumonia was observed. In group 2, 4 (10%) patients died: 1 (2.5%) patient due to ACVD, 1 (2.5%) patient due to progression of oncological process, and 22 (5%) patients due to COVID-19. Also, 2 (5.5%) and 1 (2.5%) cases of acute coronary syndrome (ACS) were observed in groups 1 and 2, respectively ($p=0.61$).
<i>Conclusion</i>	In the x-ray endovascular (group 1) and the combination (group 2) intervention groups, lethal outcomes due to myocardial infarction were absent. This fact confirms the importance of PCI in patients with CLLI for prevention of possible ACS in the long-term. Both therapeutic tactics in managing CLLI patients with IHD demonstrated high safety and clinical efficacy during the hospital and long-term periods and can be extensively used in routine clinical practice.
<i>Keywords</i>	Chronic lower limb ischemia; ischemic heart disease; cardiovascular complications
<i>For citations</i>	Alekyan B.G., Karapetyan N.G., Chupin A.V., <u>Zotikov A.E.</u> , Varava A. B., Knysh Yu.B. et al. Long-Term Results of the Treatment of Patients With Chronic Ischemia of the Lower Limbs in Combination With Ischemic Heart Disease. <i>Kardiologiia</i> . 2022;62(9):37–43. [Russian: Алесян Б.Г., Карапетян Н.Г., Чупин А.В., <u>Зотиков А.Е.</u> , Варава А.Б., Кныш Ю.Б. и др. Отдаленные результаты лечения пациентов с хронической ишемией нижних конечностей в сочетании с ишемической болезнью сердца. <i>Кардиология</i> . 2022;62(9):37–43].
<i>Corresponding Author</i>	Sedgaryan M. A. E-mail: sedgaryan@gmail.com

Chronic limb threatening ischemia (CLTI) stage IIB is a stable and slowly progressing disease that involves the development of muscle discomfort in the lower limbs and is usually described as burning, pain, or heaviness when walking a distance of less than 200 m [1]. CLTI is associated with coronary artery involvement in almost 50% of patients and cerebrovascular diseases in only 20% [2].

It is noted in the 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases that the prevalence of coronary artery disease (CAD) ranges in patients with lower limb arterial involvement from 25% to 72%, and the prevalence of lower limb atherosclerosis ranges in patients with CAD from 7% to 16% [3].

CAD and CLTI remain socially significant diseases. In 2018, Olinic et al. [2] published the data on lower limb diseases and showed that the distance of painless walking

progressively decreased within 5 years in 20% of patients with CLTI, one third of whom subsequently developed critical limb ischemia (CLI). Within a year after the diagnosis of CLI, 30% of patients have their lower limbs amputated, 20% if patients die, and only 45% survive with both lower limbs [2, 4, 5].

Jones et al. [6] note that one- and three-year all-cause mortality (including death of myocardial infarction (MI) and stroke) in patients subjected to major amputation was 48.3% and 70.9%, respectively. These data indicate the need for timely treatment of both arterial systems in order to reduce the incidence of complications and the rate of disability.

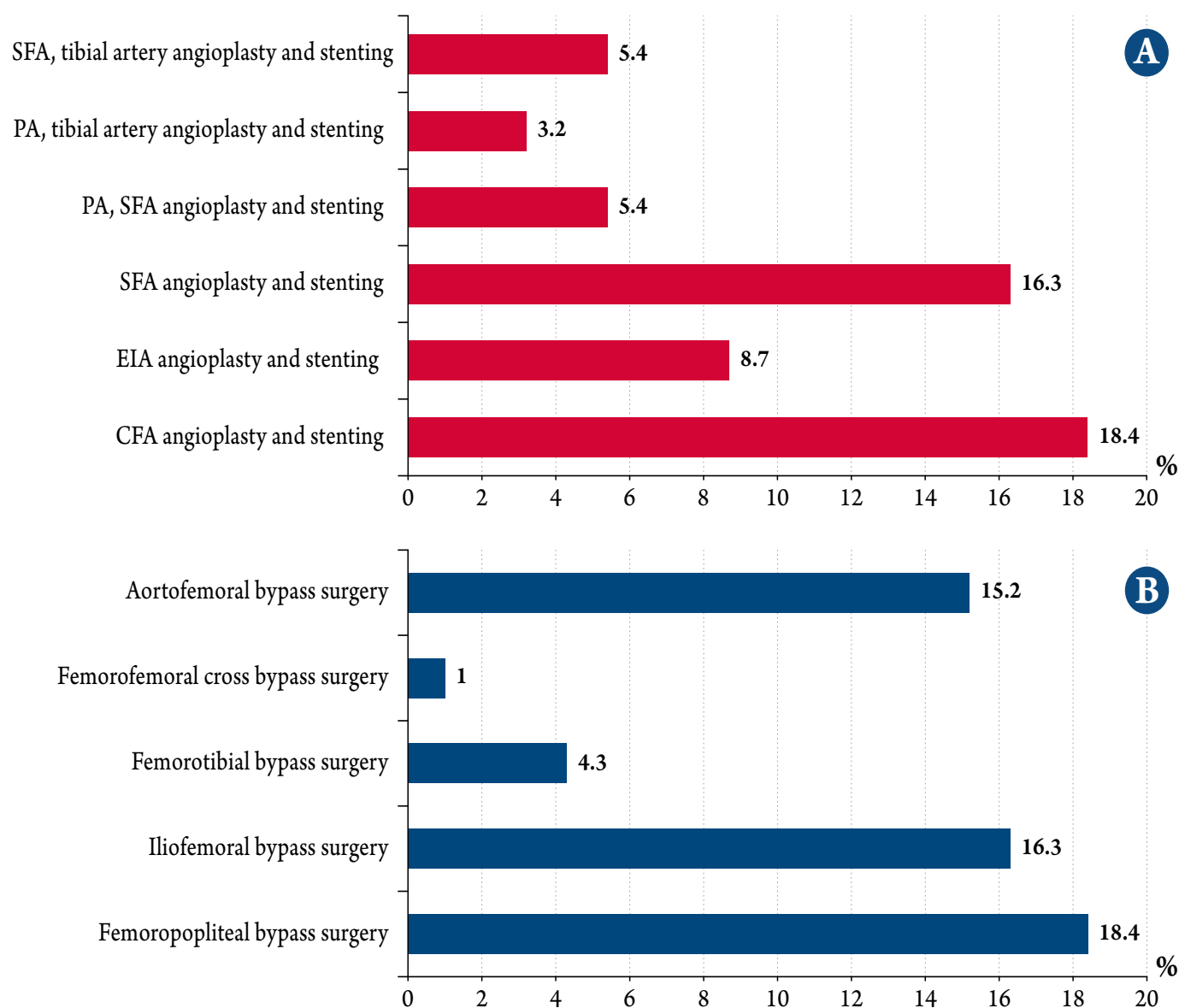
Objective

Compare the long-term outcomes of X-ray endovascular (percutaneous coronary intervention (PCI) and angioplasty

Table 1. Clinical characteristics of patients with CLTI and CAD

Clinical characteristics		PCI + lower limb arterial angioplasty (n=46)		PCI + open lower limb arterial surgery (n=46)		p
		n	%	n	%	
Age, years		67.02±7.61	–	64.46±7.70	–	0.111
Sex	male	30	65.22	40	86.96	0.015
	female	16	34.78	6	13.04	
CAD	PICS	13	28.26	13	28.26	0.817
	FC II (CCS)	19	41.3	17	36.95	
	FC III (CCS)	16	34.78	20	43.47	
	painless	11	23.91	9	19.57	
Diabetes mellitus		14	30.43	4	8.70	0.016

CLTI, chronic limb threatening ischemia;
PICS, postinfarction cardiosclerosis; CCS, Canadian Cardiovascular Society.

Figure 1. Number of surgeries performed. Primary X-ray endovascular interventions (A) and open surgeries (B) on lower limb arteries (n=53)


CIA, common iliac artery; EIA, external iliac artery; SFA, superficial femoral artery; PA, popliteal artery; CFA, common femoral artery.

with limb stenting – Group 1) and combined treatment (PCI and open limb surgery – Group 2) in patients with CLTI with concomitant CAD.

Material and methods

From January 1, 2017, to December 31, 2020, 92 patients with CLTI stage IIB with concomitant CAD were treated in A. V. Vishnevskiy National Medical Research Center for Surgery, who had not benefited from the best-possible drug therapy used to prevent the progression of atherosclerosis, manage risk factors, and increase the distance of painless walking. Ankle-brachial index (ABI) was 0.60 ± 0.13 in Group 1 and 0.54 ± 0.13 in Group 2 ($p=0.021$). The outcomes of hospital treatment have been previously published [7]. This article presents brief clinical characteristics of patients (Table 1).

The data obtained were analyzed using Statistica 7.0. The arithmetic means (M) and standard deviations (SD) were calculated. Non-normally distributed variables were compared using the Mann–Whitney U-test. Nominal data were compared using Pearson's chi-squared test. Fisher's exact test was used if there were less than 5 expected observations.

A total of 198 surgeries were performed in all 92 patients, with a mean of 2.1 surgeries per patient: 53 open surgeries and 53 X-ray endovascular interventions were performed on lower limbs, and 92 PCI procedures were performed on the coronary arteries (Figure 1) [7].

Myocardial revascularization was performed only in patients with angiographically significant coronary artery

disease (stenosis of more than 75%). The choice of a method of intervention on lower limbs was based on the 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases depending on the length of the lesion. Endovascular intervention was chosen for femoral popliteal lesions of less than 25 cm long (class I, level C) and aortoiliac lesions of less than 5 cm long (class I, level C), open surgeries were considered in other cases [3].

All patients with a history of PCI received dual antiplatelet therapy (DAPT); dosages and duration of therapy were based on the ESC guidelines [8]. Clopidogrel 75 mg and acetylsalicylic acid 100 mg were prescribed daily for 6 months with further evaluation of the cardiovascular risk and the decision whether to prolong DAPT up to 1 year followed by continuous administration of acetylsalicylic acid 100 mg.

Results

There were no major adverse cardiovascular events (death, MI, acute cerebrovascular accident (CVA)) during open surgeries and X-ray endovascular interventions [7]. The median period between hospital admissions was 133 days.

During the hospital treatment, a total of 2 minor adverse events were observed in Group 1. One (2.1%) patient experienced bradycardia and hypotension after PCI, was managed the ICU and transferred to the specialized unit after stabilization. Another patient had a hematoma at the puncture site after lower limb angioplasty [7].

Long-term treatment outcomes were evaluated in 76 (82.6%) of 92 patients based on repeated admissions

Table 2. Long-term treatment outcomes in patients with CLTI and concomitant CAD (n=76)

Complication	PCI + lower limb arterial angioplasty (n=36)		PCI + open lower limb arterial surgery (n=40)		p
	n	%	n	%	
Death:	1	2.7	4	10.0	0.61
• Complications after COVID-19	0	0	2	5.0	
• Cancer	0	0	1	2.5	
• CVA	0	0	1	2.5	
• Pneumonia	1	2.7	0	0	
MACCE:					0.61
• ACS	2	5.5	1	2.5	
• CVA	0	0	0	0	
MALE:					0.49
• Stent/shunt thrombosis	1	2.7	2	5.0	
• Amputation	0	0	1	2.5	
• Repeat lower limb artery intervention	4	11.1	1	2.5	0.13
Repeat PCI	5	13.8	3	7.5	0.13
Total	13	36.1	12	30.0	–

CLTI, chronic limb threatening ischemia; MACCE, major adverse cardiac and cerebrovascular events; MALE, major adverse limb events; CVA, acute cerebrovascular accident.

(34.9%), outpatient examinations (10.8%), demographic analysis, and telephone interviews (54.3%). The duration of the follow-up period was 34.15 ± 13.14 months in Group 1 (median 36.68 [26.52; 45.13]; 95% confidence interval (CI) 29.70–38.59) and 35.36 ± 11.53 months in Group 2 (median 32.20 [26.92; 45.72]; 95% CI 31.67–39.05; $p=0.67$). Table 2 provided the long-term outcomes of treatment.

In Group 1, 1 (2.7%) death due to non-COVID-19 pneumonia was reported. In Group 2, there were 4 (10%) fatal outcomes: 1 (2.5%) patient died of CVA, 1 (2.5%) due to the aggravation of cancer, and 2 (5%) patients died of COVID-19. There were also 2 (5.5%) and 1 (2.5%) case of ACS, respectively, in Group 1 and Group 2 ($p=0.61$).

It should be noted that there were not fatal outcomes associated with acute MI in the long-term follow-up period due to the revascularization of both vascular systems in 76 patients included in the long-term outcome analysis. According to the Kaplan-Meier survival curves, there were no significant differences ($p=0.223$) between the groups, however, there was a decrease in survival in Group 2 (PCI + open limb surgery) after 30 months of follow-up.

Discussion

The need for myocardial revascularization prior to elective limb intervention has been discussed for decades. However, there is still no consensus whether it is reasonable to perform coronary artery revascularization. The findings of large foreign studies are ambiguous and contradictory.

Alekian et al. [9] have shown that 320 (80.4%) of 398 patients enrolled with lower limb disease had at least one coronary artery with more than 50% lesion. Given these data, we continued the analysis of trials and started our study.

Raghunathan et al [10] regarded MI as the leading cause of death in patients with CLTI ($n=164$). Among patients with CLTI, two and three arterial systems were involved in 53 (32.9%) and 48 (29.3%) patients, respectively. 41 (25%) patients developed acute MI in the long term [10].

In the CARP study by McFalls et al. [11], 510 patients with aortic aneurysms and lower limb disease were randomized. Group 1 included patients who underwent coronary artery revascularization prior to elective vascular surgery ($n=258$), and Group 2 included patients who did not undergo revascularization ($n=252$). Noteworthy, 9 (3.6%) patients underwent myocardial revascularization due to unstable angina in Group 2 during hospital stay. In the long term, myocardial revascularization was conducted in 21 (8.3%) patients in this group. Despite these data, the authors conclude that the strategy of

coronary artery revascularization prior to elective lower limb vascular intervention does not improve short-term or long-term clinical outcomes. When discussing the CARP study, Landesberg et al. [12] believed that revascularization of all involved coronary arteries could prevent the development of MI and alter long-term survival.

The diagnosis of CAD in patients with CLTI is complicated by impossibility of performing stress tests due to severe pain in the lower limbs.

Our study shows that there were no deaths due to MI in the long-term follow-up period in the groups of endovascular intervention (Group 1) and combined treatment (Group 2). In this regard, we believe that the timely diagnosis of concomitant CAD and myocardial revascularization in patients with CLTI reduce the likelihood of fatal MI during hospital stay and in the long-term follow-up period.

Monaco et al. [13] evaluated 208 patients with aortoiliac involvement and aortic aneurysms facing moderate to high cardiovascular risk. Patients were divided into 2 groups: In Group 1 ($n=103$; 49.5%), patients were subjected to a stress test, based on which coronary angiography was conducted. Group 2 included 105 (50.4%) patients who underwent coronary angiography prior to the vascular surgery. According to the long-term findings, 5 (4.8%) major adverse cardiovascular events were reported in Group 1: MI in 4 (3.9%) patients and CVA in 1 (1.0%) patient. In Group 2, in which all patients underwent coronary angiography, 3 (2.8%) major adverse cardiovascular events were observed: MI in 2 (1.9%) patients and CVA in 1 (0.9%; $p=0.7$) patient. The number of deaths due to cardiovascular pathology was 12 (11.7%) and 5 (4.8%) in Group 1 and Group 2, respectively, in the long-term period ($p=0.1$). Thus, the authors concluded that coronary angiography and myocardial revascularization are beneficial for the long-term outcomes. In our study, there were also 2 (5.5%) cases of MI in the endovascular intervention group and 1 (2.7%) MI in the combination treatment group.

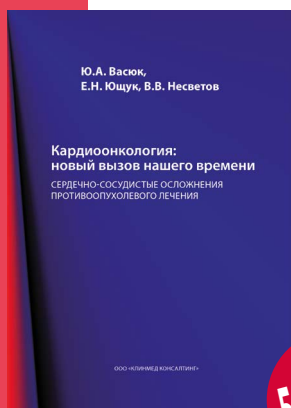
The significance of diagnosing cardiovascular diseases in patients with lower limb disease is also emphasized in the most recent 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice [14]. The 10 year incidence of coronary complications, cardiovascular mortality, and all-cause mortality doubles in patients with lower limb disease. MI or stroke develop in 20% of patients with lower limb disease within 5 years, and the mortality rate is 10–15% [14]. We suggest that timely PCI in patients with CLTI helps to avoid MI during hospital stay and significantly reduces the development of MI in



ОССН

Общество Специалистов по
Сердечной Недостаточности

Для профессионалов в области здравоохранения
ОССН и издательство «КлинМедКонсалтинг»
представляет уникальные монографии и пособия.

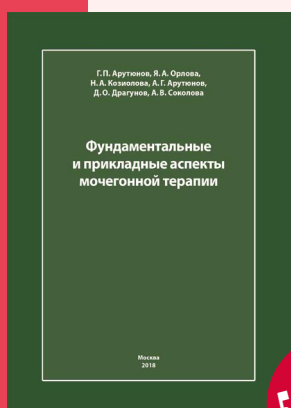


500 руб.*

Васюк Ю.А., Ющук Е.Н., Несветов В.В.

Монография «Кардиоонкология: новый вызов нашего времени. Сердечно-сосудистые осложнения противоопухолевого лечения»

В монографии описаны многие аспекты кардиоонкологии – важной дисциплинарной проблемы до настоящего времени остающейся малоизученной. Кардиотоксичность у онкологических пациентов является актуальной проблемой. Количество таких больных во всем мире неуклонно растет, а их активная противоопухолевая терапия, в том числе новыми, весьма агрессивными препаратами сопряжена с увеличением риска различных сердечно-сосудистых осложнений.



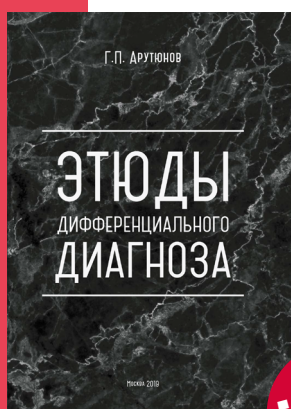
500 руб.*

Арутюнов Г.П., Орлова Я.А., Козиолова Н.А.,

Арутюнов А.Г., Драгунов Д.О., Соколова А.В.

Фундаментальные и прикладные аспекты мочегонной терапии

В данном учебном пособии описаны теоретические и прикладные аспекты мочегонной терапии. Особое внимание уделено диуретикам в лечении хронической сердечной недостаточности, артериальной гипертонии.



500 руб.*

Арутюнов Г.П.

Монография «Этюды дифференциального диагноза»

В монографии описаны навыки построения диагностической концепции на основе пропедевтического подхода к осмыслению жалоб и результатов физикального осмотра. Издание, созданное на основе личного 40-летнего опыта работы автора в многопрофильном терапевтическом стационаре будет полезно молодым специалистам, ординаторам и врачам общей практики.

Вы можете приобрести издания, обратившись в ОССН или «КлинМедКонсалтинг».

На все вопросы по заказу и доставке вам ответят по e-mail: anastasia.tarabrina@ossn.ru
или по адресу 121087, г. Москва, Береговой проезд, д.5, корп. 2, 215. Тел.: +7 (495) 765 24 28.

* – стоимость почтовых услуг по пересылке оплачивается отдельно и рассчитывается в зависимости от тарифов почты России или других служб доставки для каждого региона РФ.

the long term. According to our data, there were no deaths of MI among the 76 followed-up patients.

Thus, there is currently no consensus on the management of patients with lower limb disease and concomitant CAD, and the contradictory results of large studies demonstrate the necessity for a personalized approach and cross-disciplinary discussion of each case.

Conclusions

1. In the long-term follow-up period, among patients with chronic limb threatening ischemia and concomitant coronary artery disease who underwent percutaneous coronary intervention and revascularization of the lower limb arteries, there was only 1 (1.3%) fatal outcome associated with cardiovascular pathology (acute cerebrovascular accident). Acute coronary syndrome occurred in 3 (3.9%) patients.
2. In patients with lower limb ischemia and concomitant coronary artery disease, there were no significant differences in the outcomes of X-ray endovascular intervention and combined treatment in terms of mortality ($p>0.61$), myocardial infarction ($p>0.61$), and stroke ($p>0.61$), as well as complications of the lower limb arteries ($p>0.13$) in the long-term period after intervention.

3. According to the Kaplan – Meier survival curves, there were no significant differences ($p=0.223$) between Group 1 and Group 2, however, there was a trend to a decrease in survival in Group 2 (percutaneous coronary intervention + open limb surgery) after 30 months of follow-up.
4. It was established that there were no deaths associated with myocardial infarction in the groups of X-ray endovascular intervention (Group 1) and combined treatment (Group 2), which confirms the significance of performing percutaneous coronary intervention in patients with chronic limb threatening ischemia for the prevention of acute coronary syndrome in the long-term follow-up period.
5. Both treatment strategies for patients with chronic limb threatening ischemia and concomitant coronary artery disease show high safety and clinical efficacy in both hospital and long-term follow-up periods and can be commonly applied in daily clinical practice.

Funding

This publication had no financial support.

No conflict of interest is reported.

The article was received on 10/11/2021

REFERENCES

1. Keswani AN, Beckman JA. The Natural History of Intermittent Claudication. *Endovascular Today*. 2018;18(9):77–9. [Av. at: https://assets.bmctoday.net/evtoday/pdfs/et0919_F2_Beckman.pdf]
2. Olinic D-M, Spinu M, Olinic M, Homorodean C, Tataru D-A, Liew A et al. Epidemiology of peripheral artery disease in Europe: VAS Educational Paper. *International Angiology*. 2018;37(4):327–34. DOI: 10.23736/S0392-9590.18.03996-2
3. Aboyans V, Ricco J-B, Bartelink M-LEL, Björck M, Brodmann M, Cohnert T et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS). *European Heart Journal*. 2018;39(9):763–816. DOI: 10.1093/eurheartj/ehx095
4. Sigvant B, Lundin F, Wahlberg E. The Risk of Disease Progression in Peripheral Arterial Disease is Higher than Expected: A Meta-Analysis of Mortality and Disease Progression in Peripheral Arterial Disease. *European Journal of Vascular and Endovascular Surgery*. 2016;51(3):395–403. DOI: 10.1016/j.ejvs.2015.10.022
5. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Journal of Vascular Surgery*. 2007;45(1):S5–67. DOI: 10.1016/j.jvs.2006.12.037
6. Jones WS, Patel MR, Dai D, Vemulapalli S, Subherwal S, Stafford J et al. High mortality risks after major lower extremity amputation in Medicare patients with peripheral artery disease. *American Heart Journal*. 2013;165(5):809–815.e1. DOI: 10.1016/j.ahj.2012.12.002
7. Alekyan B.G., Pokrovskiy A.V., Karapetyan N.G., Chupin A.V., Varava A.B., Zotikov A.E. et al. Comparative Characteristics of Postoperative Outcomes of Different Treatment Strategies of Patients With Intermittent Claudication in Combination With Coronary Arteries Disease. *Kardiologiia*. 2022;62(2):28–35. [Russian: Алесян Б.Г., Покровский А.В., Карапетян Н.Г., Чупин А.В., Варава А.Б., Зотиков А.Е. и др. Сравнительная характеристика различных стратегий лечения пациентов с хронической ишемией нижних конечностей в сочетании с ишемической болезнью сердца. *Кардиология*. 2022;62(2):28–35]. DOI: 10.18087/cardio.2022.2.n1747
8. Valgimigli M, Bueno H, Byrne RA, Collet J-P, Costa F, Jeppsson A et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *European Journal of Cardio-Thoracic Surgery*. 2018;53(1):34–78. DOI: 10.1093/ejcts/ezx334
9. Alekyan B.G., Pokrovskiy A.V., Karapetyan N.G., Revishvili A.Sh. A multidisciplinary approach in determining of prevalence of coronary artery disease and treatment strategies in patients with pathology of the aorta and peripheral arteries. *Russian Journal of Cardiology*. 2019;24(8):8–16. [Russian: Алесян Б.Г., Покровский А.В., Карапетян Н.Г., Ревшвили А.Ш. Мультидисциплинарный подход в определении частоты выявления ишемической болезни сердца и стратегии лечения у пациентов с патологией аорты и периферических артерий. *Российский кардиологический журнал*. 2019;24(8):8–16]. DOI: 10.15829/1560-4071-2019-8-8-16
10. Raghunathan A, Rapp JH, Littooy F, Santilli S, Krupski WC, Ward HB et al. Postoperative outcomes for patients undergoing elective revascularization for critical limb ischemia and intermittent claudication: A subanalysis of the Coronary Artery Revascularization Prophylaxis (CARP) trial. *Journal of Vascular Surgery*. 2006;43(6):1175–82. DOI: 10.1016/j.jvs.2005.12.069
11. McFalls EO, Ward HB, Moritz TE, Goldman S, Krupski WC, Littooy F et al. Coronary-Artery Revascularization before Elective Major Vascular Surgery. *New England Journal of Medicine*. 2004;351(27):2795–804. DOI: 10.1056/NEJMoa041905
12. Landesberg G, Mosseri M. PRO: Preoperative Coronary Revascularization in High-Risk Patients Undergoing Vascular Surgery.

- Anesthesia & Analgesia. 2008;106(3):759–63. DOI: 10.1213/ane.0b013e3181685054
13. Monaco M, Stassano P, Di Tommaso L, Pepino P, Giordano A, Pina GB et al. Systematic Strategy of Prophylactic Coronary Angiography Improves Long-Term Outcome After Major Vascular Surgery in Medium - to High-Risk Patients. Journal of the American College of Cardiology. 2009;54(11):989–96. DOI: 10.1016/j.jacc.2009.05.041
 14. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. European Heart Journal. 2021;42(34):3227–337. DOI: 10.1093/eurheartj/ehab484