Zateyshchikov D. A.[1], Minushkina L. O.[2], Brazhnik V. A.[1], Galavich A. S.[3], Khasanov N. R.[3], Chichkova M. A.[2], Kosmacheva E. D.[4], Tereshchenko S. N.[5], Koziolova N. A.[6], Glezer M. G.[7], Boeva O. I.[8], Khorolets E. V.[9], Konstantinov V. O.[10]

[1] City clinical hospital №51 of State healthcare agency Moscow, Russia

[2] Central State Medical Academy of Department of Presidential Affairs, Moscow, Russia

[3] Kazan State Medical University, Kazan, Russia

[4] Kuban State Medical University, Krasnodar, Russia

[5] National Medical Research Center of Cardiology of the Ministry of Health of the Russian Federation, Moscow, Russia

[6] Perm State Medical University, Perm, Russia

[7] First Moscow State Medical University named after I.M. Sechenov, Moscow, Russia

[8] Stavropol State Medical University, Stavropol, Russia

[9] Rostov State Medical University, Rostov-on-Don, Russia

[10] North-West State Medical University named after I.I. Mechnikov, St. Petersburg, Russia

Changes in the management of patients with acute coronary syndrome – have the disease outcomes changed?

Aim	To analyze results of changing the management tactics in patients with acute coronary syndrome (ACS) in clinical practice from 2004 through 2018 expressed as improvement in prognosis.
Material and methods	Results of two observational studies were analyzed: ORACLE I (2004–2007), which included 1193 patients with ACS (mean age, 61.1±11.69 years; men, 63.3%) and ORACLE II (2014–2017), which included 1652 patients from 4 vascular centers (mean age, 64.61±12.67 years; men, 62.3%).
Results	Patients included into the ORACLE II study in 2014 were significantly older and the proportion of patients with diabetes mellitus was greater than in the ORACLE I study (14.7 and 22.6%, respectively). After matching the groups by major clinical characteristics, it was found that introducing the invasive management tactics for ACS patients was associated with a reduced rate of all-cause death (from 8.2 to 6.1% for one year), a tendency towards decreased number of coronary death cases (from 5.6 to 4.0%), and a decrease in risk of recurrent coronary complications (from 17.4 to 7.7%).
Conclusion	Implementing the vascular program statistically significantly decreased the total death rate for at least one-year observation in comparable patient groups.

Keywords	Acute coronary syndrome; all-cause death; revascularization; vascular program
For citation	Zateyshchikov D.A., Minushkina L.O., Brazhnik V.A., Galyavich A.S., Khasanov N.R., Chichkova M.A. et al. Changes in the management of patients with acute coronary syndrome – have the disease outcomes changed? Kardiologiia. 2020;60(9):30–37. [Russian: Затейщиков Д.А., Минушкина Л.О., Бражник В.А., Галявич А.С., Хасанов Н.Р., Чичкова М.А. и др. Изменение тактики ведения больных с острым коронарным синдромом – изменились ли исходы заболевания? Кардиология. 2020;60(9):30–37].

Corresponding author	Minushkina L.O. E-mail: minushkina@mail.ru

Introduction

A vascular disease management program has been implemented recently in most regions of the Russian Federation; a significant number of patients with acute coronary syndrome (ACS) have been subjected to invasive examination and treatment. Drug therapy possibilities have also increased: new antiplatelet agents, anticoagulants, and other drugs have been developed and are in use. Lipid-lowering drugs (mainly statins) come into wide use. The new treatment standards have been expected to improved prognosis for patients. Observational studies are useful for monitoring the efficacy of new drugs and invasive treatments in real-world practice. In 2004–2007, the Russian multicenter observational study of patients with ACS ORACUL (Exacerbation of Coronary Artery Disease: Logical Probabilistic Methods of Predicting the Course to Improve the Treatment) was organized and included about 1,200 patients. In 2014, the inclusion of patients in the ORACUL II study began. Based on the findings of these two studies, we are able to analyze the differences in patient management tactics and treatment outcomes in the practice of the new invasive treatment strategy and changes in drug therapy.

ISSN 0022-9040. Kardiologiia. 2020;60(9). DOI: 10.18087/cardio.2020.9.n1172

Objective

Analyze whether changes introduced to real-world management tactics in patients with ACS from 2004 to 2014 improved the prognosis for such patients.

Materials and Methods

This study analyzes the results of two open-label multicenter observational studies organized by the Department of Therapy, Cardiology, and Functional Diagnostics with the Department of Nephrology at the Central State Medical Academy of Administration of the President of the Russian Federation.

The study entailed a comparative analysis of the results of two Russian multicenter observational studies, ORACUL I and ORACUL II (Exacerbation of Coronary Artery Disease: Logical Probabilistic Methods of Predicting the Course to Improve the Treatment), and included patients with a history of ACS. The ORACUL I study was conducted in 2004–2007 A total of 1,193 patients with ACS were included and followed up in 16 sites in 7 cities (Moscow, Chelyabinsk, Kazan, Perm, Stavropol, Rostov-on-Don, St. Petersburg) for 12 months. The study included patients with ACS with ST-segment elevation (STE-ACS) and without ST elevation (NSTE-ACS) in the presence of symptoms caused by ACS (duration of symptom by the time of hospitalization not more than 72 hours). Follow-up began on the 10th day from the onset of ACS. Recurrence of myocardial infarction (MI) or repeated episodes of myocardial ischemia lasting for more than 10 minutes delayed the patient's inclusion for another 10 days. The inclusion criteria have been described previously [1].

The ORACUL II study included patients with STE-ACS and NSTE-ACS with indications for percutaneous coronary intervention (PCI) due to the index episode. A total of 1,782 patients were included at 4 sites (in Moscow, Kazan, Astrakhan, and Krasnodar) in which the vascular disease management program was implemented. In the ORACUL II study, patients were followed up from the onset of ACS symptoms. However, patients who died within 10 days from the onset of ACS and those who were followed up for less than 10 days were excluded from the analysis to unify follow-up duration. Data of 1,652 patients were used for the analysis. The inclusion criteria used in the ORACUL II study have been described earlier [2].

Data on adverse outcomes were collected at control examinations or phone calls made on days 25, 90, 180, and 360 after the inclusion in the study. The primary endpoint was all-cause death. All cases of coronary death, coronary complications (death and repeated episodes of ACS), and all cases of strokes were analyzed.

The local ethics committees of the investigational sites approved the study. Before inclusion in the study, all subjects signed written informed consent.

Statistical processing of the findings was performed using statistical software suites SPSS 23.0, MedCalc 19.0.3, and NCSS 200919.0.2. Analysis of the distribution and criteria of its normality was carried out for the extensive variables. Since the distribution of all the parameters studied was not normal, non-parametric methods of calculation were used for the analysis. The means and standard errors (M ± m) were calculated for the extensive variables. Discrete values were compared using Pearson's chi-square test. The differences were statistically significant at $p<0.05$.

Pseudo-randomization was used to match patient groups of the ORACUL I and ORACUL II studies according to clinical signs. The propensity score was calculated using the logistic regression method. The groups were matched using 1:1 nearest-neighbor matching taking into account the presence of diabetes mellitus (DM) as the main parameter; age, sex, coronary artery disease (CAD), history of MI, and chronic heart failure (CHF) were assessed as covariates.

The percentage meta-analysis was carried out using the Freeman–Tukey transformed proportions to calculate a weighted cumulative percentage using the fixed and random-effect model. The Q and I^2 criteria were used to evaluate the heterogeneity of the model.

Results

The clinical characteristics of patients included in the ORACUL I and ORACUL II studies are provided in Table 1.

The patient cohorts have several significant differences. Patients registered in 2014–2017 were significantly older, with a mean age difference of about 3.5 years. The percentage of patients with DM increased significantly. In the ORACUL II study, patients were more likely to have a history of CAD before inclusion in the study, and the rate of MI did not differ. Moreover, arterial hypertension, peripheral atherosclerosis, and conduction disorders were more common. CHF was slightly rarer. In the ORACUL II study, the rate of alcohol consumption was higher, and the rate of smoking was lower. There were no statistically significant differences in sex, body mass index, and glomerular filtration rate. The percentage of patients with STE-ACS did not differ significantly.

Treatment of patients in the two studies was expectedly different. PCI for the index event was performed in 57.4% of patients followed up in 2014–2017, including 75.8% of patients with STE-ACS and 50.1% of patients with NSTE-ACS. In 2004–2007, such interventions were not routine. The analysis of drug therapy showed that the percentage of patients who received antiplatelet drugs, beta-blockers, and renin-angiotensin system inhibitors increased. The percentage of patients who received statins almost doubled by the time of the discharge from hospital (45.6% vs. 91.9%, respectively; $p<0.001$). The percentage of patients who received nitrates and cardiac glycosides decreased. More

Table 1. Comparative clinical characteristics of patients in the ORACUL I and ORACUL II studies

Parameter	ORACUL I	ORACUL II	p
	All patients (n = 1,193)	All patients (n = 1,652)	
Male/female, n (%)	755 (63.3%)/438 (36.7%)	1029 (62.3%)/623 (37.7%)	0.585
Age at inclusion, years	61.1±11.69	64.61±12.672	0.0001
BMI, kg/m^2	28.1±4.51	28.48±4.980	0.09
STE-ACS, abs. (%)	480 (40.2%)	611 (37%)	0.082
Elevated markers of myocardial damage during index event, n (%)	52.8% (n = 630) of all patients, 78.2% of patients with the known level	69.4% (n = 1143) of all patients, 91.4% of patients with the known level	0.001 0.001
History of CAD, n (%)	806 (67.6%)	1192 (72.2%)	0.007
History of MI, n (%)	384 (32.2%)	496 (30%)	0.209
History of hypertension, n (%)	973 (81.6%)	1458 (88.3%)	0.0001
History of stroke, n (%)	108 (9.1%)	188 (11.4%)	0.0472
CHF before current hospitalization, n (%)	651 (54.6%)	829 (50.4%)	0.0265
Peripheral atherosclerosis, n (%)	150 (12.6%)	428 (25.9%)	0.0001
Diabetes mellitus, n (%)	175 (14.7%)	373 (22.6%)	0.0001
History of AV block, n (%)	18 (1.5%)	73 (4.4%)	0.001
Bundle branch block, n (%)	66 (5.5%)	140 (8.5%)	0.002
AF within the first 10 days from the onset of ACS, n (%)	34 (2.8%)	65 (3.9%)	0.1114
Smoking, n (%)	458 (38.4%)	465 (28.1%)	0.0001
Alcohol consumption, n (%)	342 (28.7%)	778 (47.1%)	0.0001
Therapy	**Day 10**	**Discharge**	–
Antiplatelet drugs, n (%)	1109 (93,0%)	1595 (96,5%)	0,001
Nitrates, n (%)	714 (59,9%)	220 (13,3%)	0,0001
Beta-blockers, n (%)	966 (81,0%)	1449 (87,7%)	0,0001
ACE inhibitors/sartans, n (%)	1014 (85%)	1473 (89,2%)	0,0008
Statins, n (%)	544 (45,6%)	1518 (91,9%)	0,001
Calcium antagonists, n (%)	144 (12,1%)	382 (23,1%)	0,0001
Diuretics, n (%)	370 (31,0%)	611 (37,0%)	0,0009
Cardiac glycosides, n (%)	33 (2,8%)	4 (0,2%)	0,001
Antiarrhythmic agents, n (%)	35 (2,9%)	86 (5,2%)	0,0026
Warfarin, n (%)	20 (1,7%)	92 (5,6%)	0,001
Dabigatran, n (%)	–	16 (1,0%)	–
Rivaroxaban, n (%)	–	20 (1,2%)	–
Apixaban, n (%)	–	6 (0,5%)	–
Heparin, n (%)	44 (3,7%)	101 (6,1%)	0,004
PCI for index event, n (%)	–	952 (57,4%) STE-ACS 75.8%, NSTE-ACS 50.1%	–
GFR, mL/min/1.73m^2	73.4±26.52	71.98±33.960	0.0564
Outcomes (days 10 to 366 from ACS)			
All-cause death, n (%)	98 (8.2%)	138 (8.4%)	0.848
Coronary death, n (%)	67 (5.6%)	89 (5.4%)	0.817
All coronary complications, n (%)	208 (17.4%)	144 (8.7%)	0.001
Stroke, n (%)	16 (1.3%)	34 (2.05%)	0.130

BMI, body mass index; STE-ACS, acute coronary syndrome with ST segment elevation; CAD, coronary artery disease; MI, myocardial infarction; CHF, chronic heart failure; AV, atrioventricular; AF, atrial fibrillation; ACE, angiotensin-converting enzyme; PCI, percutaneous intervention GFR, glomerular filtration rate.

ISSN 0022-9040. Kardiologiia. 2020;60(9). DOI: 10.18087/cardio.2020.9.n1172

Table 2. Clinical characteristics and outcomes in the ORACUL I and ORACUL II studies after matching by risk factors

Parameter	ORACUL I (%), n = 1,192	ORACUL II (%), n = 1,192	p
Age, years	61.32±11.69	61.81±11.92	0.786
Male, n (%)	754 (63.3%)	766 (64.3%)	0.609
Diabetes mellitus, n (%)	175 (14.7%)	175 (14.7%)	1.000
Hypertension, n (%)	972 (81.5%)	1,002 (84.0%)	0.07
History of myocardial infarction, n (%)	384 (32.2%)	370 (31.0%)	0.538
CAD prior the index event, n (%)	805 (67.5%)	836 (70.1%)	0.170
History of CVA, n (%)	108 (9.1%)	107 (9.7%)	0.446
History of CHF, n (%)	651 (54.6%)	612 (48.5%)	0.110
Smoking, n (%)	458 (38.4%)	408 (34.2%)	0.05
Outcomes (days 10 to 366 from ACS)			
All-cause death	98 (8.2%)	67 (6.1%)	0.048
Coronary death	67 (5.6%)	44 (4.0%)	0.079
All coronary complications	208 (17.4%)	73 (7.7%)	0.0001
Stroke	16 (1.3%)	24 (2.1%)	0.171

CAD, coronary artery disease; CVA, cerebrovascular accident; CHF, chronic heart failure.

patients received anti-arrhythmic drugs and anticoagulants. Besides the increased number of patients receiving warfarin, there were patients administered new oral anticoagulants (dabigatran, rivaroxaban, and apixaban).

In general, all-cause mortality and the incidence of coronary complications and strokes did not differ significantly between the two studies in the adverse outcomes reported in the follow-up year. The only variable that decreased significantly was the incidence of all coronary complications (death and non-fatal repeated ACS episodes).

Taking into account the significant differences in the incidence of conditions that are risk factors (RFs) of adverse outcomes (DM, CAD, CHF, hypertension, smoking) and the significant differences between the age groups of patients in the two followed-up cohorts, a procedure of propensity score matching was performed using pseudo-randomization to compare the incidence of adverse outcomes. The result was 1,192 pairs of patients. The main clinical characteristics and the rate of adverse outcomes are shown in Table 2. There were no significant differences in age and major risk factors after matching (Table 2).

The pseudo-randomization procedure produced two homogeneous samples, which did not differ in the rate of RFs of the main adverse outcomes. Analysis of the adverse outcome rates showed that, following the introduction of invasive tactics for the management of patients with ACS, all-cause mortality decreased significantly within a year (from 8.2% to 6.1%), and there was also a tendency toward a decrease in the rate of coronary death (from 5.6% to 4.0%). The number of recurrent coronary complications decreased significantly. The stroke rate was slightly higher in the ORACUL II study, but the differences were not significant.

Given a wide variety of data on long-term outcomes in patients with ACS after discharge from hospital, and in order to assess the homogeneity of the available data, we performed a meta-analysis of observational studies in which long-term outcomes were evaluated. The studies were selected from the PubMed database using the keywords «acute coronary syndrome», «death», and «registry» from 2017 to 2019.

Table 3. Characteristics of studies included in the meta-analysis

Study	Number of patients	Age, years	Number of patients subjected to PCI, %	12-month mortality
PROMETHEUS study [3]	19914	63±12.9	100	963
Korea Acute Myocardial Infarction Registry–National Institutes of Health [4]	9 684	–	77.9	517
Australia multicenter registry [5]	13 184	64±11.5	100	775
START-ANTIPLATELET [6]	840	67±13	85	62
BleeMacs [7]	4520	66±11	56	259
ORACUL II	1652	64±11	60	138
RECORD 3 [8]	966	64±11.9	44.3	81
GReek AntiPlatElet registry [9]	2047	62±12	100	98
Oman PCI Registry [10]	926	58±11.2	100	46
STARS-1 Program [11]	2233	56±13	42.5	181

PCI, percutaneous coronary intervention.

Studies were selected that contained data on the 12-month all-cause mortality after ACS. Characteristics of the selected studies are detailed in Table 3.

A total of 55,966 patients were included in the meta-analysis. The 12-month mortality was 5.5% for a fixed model (Figure 1). The data of all studies were within 95% confidence interval, and their distribution was symmetrical and homogeneous (Figure 2).

Discussion

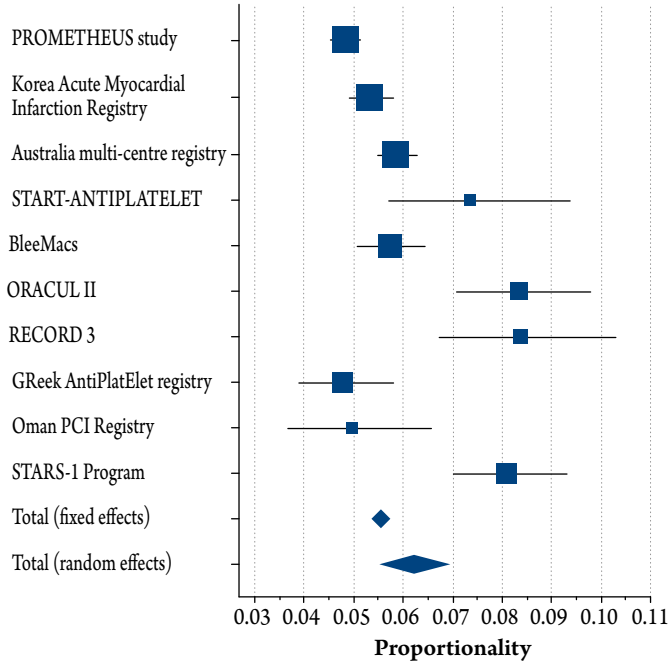
The resulting data provide evidence of changes in the management of patients with ACS after implementation of the vascular disease management program, which made invasive procedures for ACS more accessible. It should be noted that the demographic characteristics of patients in the two comparable studies changed as well as the approaches to treatment (availability of interventions, common use of statins, new groups of antiplatelet and anticoagulant drugs). Introduction of the invasive strategy of patient management resulted in hospitalizations of patients with higher-risk ACS. In the ORACUL II study, patients were older and had a more unfavorable RF profile (a large percentage of patients with CAD, peripheral atherosclerosis, DM). The problem of an increasing number of patients with DM has already been closely analyzed [12]. The increased percentage of patients with DM has been shown in all age groups. This may be due to both the improvement of diagnosis and actual increasing numbers of such patients. The percentage of patients with peripheral atherosclerosis also increased. This change is likely to be associated with both the older age of patients and increased availability of diagnostic studies.

All-cause mortality was relatively high (about 8%) in both studies ORACUL I and ORACUL II. Similar all-cause mortality was contained in the Russian register RECORD-3 (8.4%), in which patients were included in March – April 2015, and in the 2015–2017 Middle-East register of ACS, where 12-month all-cause mortality after ACS was 8.1%. However, it should be noted that the patient population was significantly younger (mean age 56 years old) in the latter than in our study [11].

In the Australian ACS register, similar to our study in terms of age of included patients, 12-month mortality was the highest in patients with STE-ACS (8.7%), lower in patients with NSTE-ACS (4.5%), and the lowest in patients with unstable angina [5]. Our study included only high- and intermediate-risk patients, with a small percentage of patients without elevated cardiac-specific enzymes, which partly explains the relatively high 12-month mortality rate.

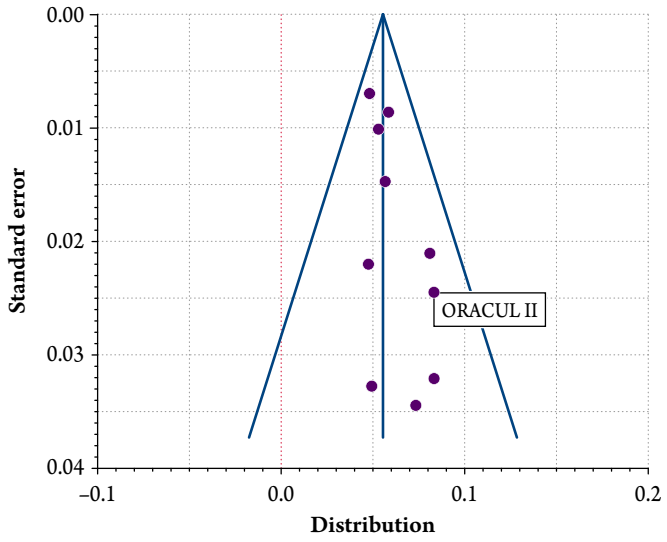
In the Greek ACS register similar to the ORACUL II study according to the clinical characteristics of patients, all-cause mortality was 4.8% [9], which is lower than in our study. However, all patients underwent revascularization in the Greek register; the percentage of such patients was only about 57% in the ORACUL II register. In general, our meta-analysis showed that, despite the fact that the 12-month mortality rate of patients after ACS was higher in our study than in most foreign registers, the inclusion of our data in the meta-analysis did not violate the homogeneity and correctness of data distribution.

Figure 1. Meta-analysis data on all-cause mortality within 12 months of follow-up after ACS



ACS, acute coronary syndrome.

Figure 2. Distribution of meta-analysis data on all-cause mortality after ACS



ACS, acute coronary syndrome.

ISSN 0022-9040. Kardiologiia. 2020;60(9). DOI: 10.18087/cardio.2020.9.n1172

ПРЕСТАНС®

ПЕРИНДОПРИЛ + АМЛОДИПИН

1 ТАБЛЕТКА В ДЕНЬ

ВЫРАЖЕННОЕ СНИЖЕНИЕ АД

ТОЧНОЕ ПОПАДАНИЕ В ЦЕЛЬ

Рег. уд. N ЛСР-000836/10

На правах рекламы

Краткая инструкция по медицинскому применению препарата Престанс®

СОСТАВ*. Престанс в таблетках 5 мг/5 мг, 5 мг/10 мг, 10 мг/5 мг, 10 мг/10 мг, содержащих соответственно периндоприла аргинина (ПЕР) 5 мг/амлодипина (АМЛО) 5 мг, ПЕР 5 мг/АМЛО 10 мг, ПЕР 10 мг/АМЛО 5 мг, ПЕР 10 мг/АМЛО 10 мг. Содержит лактозу в качестве вспомогательного вещества. **ПОКАЗАНИЯ К ПРИМЕНЕНИЮ*.** Артериальная гипертензия и/или ишемическая болезнь сердца (ИБС): стабильная стенокардия напряжения у пациентов, которым требуется терапия периндоприлом и амлодипином. **СПОСОБ ПРИМЕНЕНИЯ И ДОЗЫ*.** Внутрь по 1 таблетке 1 раз в сутки утром перед приемом пищи. При необходимости доза препарата может быть изменена или может быть проведен подбор доз отдельных компонентов. *Пациенты пожилого возраста и пациенты с почечной недостаточностью.* Регулярно контролировать концентрацию креатинина и калия (K^+) в плазме крови. Противопоказан пациентам с клиренсом креатинина (КК) менее 60 мл/мин. *Пациенты с печеночной недостаточностью.* Поиск начальной и поддерживающей дозы проводить индивидуально, применяя амлодипин и периндоприл в монотерапии. *Дети и подростки.* Не назначать. **ПРОТИВОПОКАЗАНИЯ*.** Повышенная чувствительность к действующим веществам, или другим ингибиторам АПФ, или другим производным дигидропиридина, или к любому вспомогательному веществу в составе препарата; ангионевротический отек в анамнезе на фоне терапии ингибитором АПФ; наследственный/идиопатический ангионевротический отек; беременность и период грудного вскармливания (см. раздел «Применение при беременности и в период грудного вскармливания»); совместное применение с алискиреном и лекарственными препаратами, содержащими алискирен, у пациентов с сахарным диабетом и/или умеренными или тяжёлыми нарушениями функции почек (СКФ <60 мл/мин/1,73м^2 площади поверхности тела (см. разделы «Взаимодействие с другими лекарственными средствами» и «Фармакодинамика»); совместное применение с антагонистами рецепторов ангиотензина II (АРА II) у пациентов с диабетической нефропатией; совместное применение с комбинированными лекарственными препаратами, содержащими валсартан + сакубитрил (см. разделы «Взаимодействие с другими лекарственными средствами» и «Особые указания»); экстракорпоральная терапия, ведущая к контакту крови с отрицательно заряженными поверхностями (см. раздел «Взаимодействие с другими лекарственными средствами»); выраженный двусторонний стеноз почечных артерий или стеноз артерии единственной функционирующей почки (см. раздел «Особые указания»); тяжелая артериальная гипотензия (САД менее 90 мм рт.ст.); шок (включая кардиогенный); обструкция выходного тракта левого желудочка (например, выраженный стеноз устья аорты); гемодинамически нестабильная сердечная недостаточность после острого инфаркта миокарда; почечная недостаточность (КК менее 60 мл/мин); возраст до 18 лет, наследственная непереносимость галактозы, лактазная недостаточность и глюкозо-галактозная мальабсорбция. **ОСОБЫЕ УКАЗАНИЯ*.** *Повышенная чувствительность/ангионевротический отек.* Прием препарата должен быть прекращен, пациент должен наблюдаться до полного исчезновения признаков отека. Ангионевротический отек с отеком гортани может привести к летальному исходу. При совместном применении с ингибиторами mTOR повышается риск ангионевротического отека. *Совместное применение с препаратами, содержащими валсартан + сакубитрил.* Противопоказано. Применение одного препарата не ранее чем через 36 часов после прекращения приема другого. *Анафилактоидные реакции при проведении афереза ЛПНП.* В редких случаях могут развиваться угрожающие жизни реакции. Временно прекратить терапию перед каждой процедурой. *Анафилактоидные реакции при проведении десенсибилизации.* Временно прекратить терапию перед каждой процедурой. При случайном приеме препарата анафилактоидная реакция возникала снова. *Нейтропения/агранулоцитоз/тромбоцитопения/анемия.* С крайней осторожностью применять периндоприл у пациентов с системными заболеваниями соединительной ткани, на фоне приема иммунодепрессантов, аллопуринола или прокаинамида. Контролировать лейкоциты в крови. *Реноваскулярная гипертензия.* У пациентов с двусторонним стенозом почечных артерий или артерии единственной почки возрастает риск развития тяжелой гипотензии и почечной недостаточности. Прием диуретиков – дополнительный фактор риска. Ухудшение функции почек возможно при незначительном изменении концентрации креатинина у пациентов с односторонним стенозом почечной артерии. *Двойная блокада РААС.* Совместное применение ингибиторов АПФ с АРА II или алискиреном повышает риск гипотензии, гиперкалиемии и нарушения функции почек (включая острую почечную недостаточность). Поэтому двойная блокада РААС не рекомендуется. Противопоказано применение ингибиторов АПФ в сочетании с АРА II у пациентов с диабетической нефропатией. *Беременность.* Прекратить лечение. При необходимости назначить другую гипотензивную терапию. *Первичный гиперальдостеронизм.* Прием препарата не рекомендуется. *Артериальная гипотензия.* У пациентов с повышенным риском развития симптоматической артериальной гипотензии и у пациентов со стенокардией и цереброваскулярными заболеваниями необходимо тщательно контролировать АД, функцию почек и содержание K^+ в сыворотке крови. Преходящая артериальная гипотензия не является препятствием для дальнейшего приема препарата. После восстановления объема циркулирующей крови и АД лечение может быть продолжено. *Митральный стеноз/аортальный стеноз/гипертрофическая кардиомиопатия.* С осторожностью. *Нарушение функции почек.* Пациентам с КК менее 60 мл/мин рекомендуется индивидуальный подбор доз периндоприла и амлодипина и необходим регулярный контроль содержания K^+ и креатинина в сыворотке крови. У пациентов со стенозом почечных артерий возможно повышение мочевины и креатинина в крови. Наличие реноваскулярной гипертензии обусловливает повышенный риск тяжелой гипотензии и почечной недостаточности. Амлодипин не выводится посредством диализа. *Печеночная недостаточность.* В редких случаях на фоне ингибиторов АПФ возникает холестатическая желтуха. При прогрессировании развивается фульминантный некроз печени, иногда с летальным исходом. При появлении желтухи или значительного повышения «печеночных» ферментов прекратить прием препарата. При тяжелой печеночной недостаточности повышать дозу постепенно, обеспечивая мониторинг состояния. *Этнические различия.* Периндоприл, возможно, оказывает менее выраженное действие у пациентов негроидной расы. У них чаще развивается ангионевротический отек. *Сухой кашель. Хирургическое вмешательство/анестезия.* Прекратить лечение за сутки до операции. *Гиперкалиемия.* Регулярный контроль K^+ в крови у пациентов старше 70 лет, с почечной недостаточностью, ухудшением функции почек, сахарным диабетом, дегидратацией, острой декомпенсацией сердечной недостаточности, метаболическим ацидозом, совместным применением K^+-сберегающих диуретиков, солей K^+. *Сахарный диабет.* В течение первого месяца терапии контролировать глюкозу в крови. *Сердечная недостаточность.* С осторожностью. *Гипертонический криз.* Эффективность и безопасность не установлены. *Пожилые пациенты.* Увеличение дозы с осторожностью. **ВЗАИМОДЕЙСТВИЕ С ДРУГИМИ ЛЕКАРСТВЕННЫМИ СРЕДСТВАМИ*.** *Совместное применение противопоказано.* Алискирен: у пациентов с сахарным диабетом и/или нарушением функции почек (СКФ <60 мл/мин). Экстракорпоральная терапия. Валсартан + сакубитрил. *Нерекомендуемые комбинации:* алискирен: у пациентов, не имеющих диабета или нарушения функции почек; АРА II, эстрамустин, ко-тримоксазол (сульфаметоксазол + триметоприм), K^+-сберегающие диуретики (триамтерен, амилорид), соли K^+, препараты лития, дантролен (внутривенное введение), грейпфрут или грейпфрутовый сок. *Сочетания, требующие особого внимания:* гипогликемические средства (инсулин, производные сульфонилмочевины), K^+-несберегающие диуретики, K^+-сберегающие диуретики (эплеренон, спиронолактон), рацекадотрил, ингибиторы mTOR (сиролимус, эверолимус, темсиролимус), нестероидные противовоспалительные препараты, включая ацетилсалициловую кислоту ≥3 г/сут, алтеплаза, индукторы и ингибиторы CYP3A4, баклофен. *Сочетания, требующие внимания:* глиптины (линаглиптин, саксаглиптин, ситаглиптин, вилдаглиптин), симпатомиметики, препараты золота, аллопуринол, прокаинамид, такролимус, циклоспорин, симвастатин, гипотензивные средства, вазодилататоры, кортикостероиды, тетракозактид, α-адреноблокаторы (празозин, альфузозин, доксазозин, тамсулозин, теразозин), амифостин, трициклические антидепрессанты, нейролептики, средства для общей анестезии. **ПРИМЕНЕНИЕ ПРИ БЕРЕМЕННОСТИ И В ПЕРИОД ГРУДНОГО ВСКАРМЛИВАНИЯ*.** Противопоказан. **ФЕРТИЛЬНОСТЬ*. ВЛИЯНИЕ НА СПОСОБНОСТЬ УПРАВЛЯТЬ ТРАНСПОРТНЫМИ СРЕДСТВАМИ, МЕХАНИЗМАМИ*.** Возможно вследствие головокружения, сонливости и других побочных реакций. **ПОБОЧНОЕ ДЕЙСТВИЕ*.** *Очень часто:* отеки. *Часто:* сонливость, головокружение, головная боль, дисгевзия, парестезия, нарушения зрения (включая диплопию), звон в ушах, вертиго, ощущение сердцебиения, «приливы» крови к коже лица, артериальная гипотензия, одышка, кашель, боль в животе, тошнота, рвота, диспепсия, изменение частоты и характера стула, диарея, запор, кожный зуд, экзантема, кожная сыпь, припухлость в области суставов (припухлость в области лодыжек), спазмы мышц, повышенная утомляемость, астения. *Нечасто:* ринит, зозинофилия, гиперчувствительность, гипогликемия, гиперкалиемия, гипонатриемия, бессонница, лабильность настроения, депрессия, нарушение сна, тремор, гипестезия, обморочные состояния, тахикардия, аритмия, васкулит, бронхоспазм, сухость во рту, ангионевротический отек лица, конечностей, губ, слизистых оболочек, языка, голосовых складок и/или гортани, алопеция, пурпура, изменение цвета кожи, повышенная потливость, крапивница, реакции фоточувствительности, пемфигоид, артралгия, миалгия, боль в спине, нарушение мочеиспускания, никтурия, поллакиурия, почечная недостаточность, эректильная дисфункция, гинекомастия, периферические отеки, боль в грудной клетке, боль, недомогание, лихорадка, увеличение массы тела, снижение массы тела, повышение концентрации мочевины и креатинина в крови, падение. *Редко:* спутанность сознания, обострение псориаза, повышение концентрации билирубина в крови, повышение активности «печеночных» ферментов. *Очень редко:* лейкопения/нейтропения, агранулоцитоз, панцитопения, тромбоцитопения, гемолитическая анемия у пациентов с врождённой недостаточностью глюкозо-6-фосфатдегидрогеназы, гипергликемия, гипертонус, периферическая нейропатия, инсульт, стенокардия, инфаркт миокарда, эозинофильная пневмония, гиперплазия десен, панкреатит, гастрит, гепатит, желтуха, цитолитический или холестатический гепатит, повышение активности «печеночных» ферментов, ангионевротический отек (отек Квинке), многоформная эритема, синдром Стивенса-Джонсона, эксфолиативный дерматит, острая почечная недостаточность, снижение гемоглобина и гематокрита. *Неуточненной частоты:* экстрапирамидальные расстройства, синдром Рейно, токсический эпидермальный некролиз. Синдром неадекватной секреции антидиуретического гормона можно считать очень редким осложнением, связанным с ингибиторами АПФ. **ПЕРЕДОЗИРОВКА*. ФАРМАКОЛОГИЧЕСКИЕ СВОЙСТВА*. ФАРМАКОДИНАМИКА*** Периндоприл – ингибитор фермента, превращающего ангиотензин I в ангиотензин II (ингибитор АПФ). Амлодипин – блокатор «медленных» кальциевых каналов, производное дигидропиридина, ингибирует трансмембранный переход ионов кальция в кардиомиоциты и гладкомышечные клетки сосудистой стенки. **ФОРМА ВЫПУСКА*.** 29/30 таблеток x 1/3 (флакон + дозатор), 5 мг + 5 мг, 10 мг + 10 мг, 5 мг + 10 мг, 10 мг + 5 мг. **Регистрационное удостоверение:** ЛСР-000836/10.

**Для получения полной информации, пожалуйста, обратитесь к инструкции по медицинскому применению лекарственного препарата.*

125196, РФ, Москва, ул. Лесная, д. 7, этаж 7/8/9.
Тел.: +7 (495) 937-07-00, факс: +7 (495) 937-07-01
www.servier.ru

SERVIER

The routine use of revascularization procedures and the increased possibilities of drug therapy significantly reduced the risk of repeated coronary complications, but the risks of all-cause death and coronary death remained at the same level, which appears to be due to the differences in demographic characteristics.

Drug therapy can significantly influence the long-term prognosis after an acute episode of CAD as well as revascularization procedures. The American ACS register PROMETHEUS showed that the best possible drug therapy after the discharge from hospital contributes to a decrease in all-cause mortality within a year to 3.5% versus 9.2% in patients who did not receive full-fledged drug therapy [3]. We only analyzed the therapy administered after the discharge from hospital in this study. Treatment compliance after discharge seems essential.

Patients were matched by the main different RFs to compare the findings of the two studies. We found that total mortality was significantly lower, the total number of coronary complications was significantly decreased, and coronary mortality tended to reduce in the ORACUL II study. Despite the matching of the groups according to the main characteristics, some differences (high rate of hypertension, peripheral atherosclerosis) remained.

The distinguishing factor of this work is that the inclusion criteria were different in the ORACUL I and ORACUL II studies. The inclusion criteria of ORACUL II allowed for including initially more severe high- and intermediate-risk patients who had indications of PCI during the current hospital stay. This may explain why, amid the change in management tactics, a significant reduction in coronary mortality was not demonstrated. At the same time, highly reliable differences in the rate of repeated coronary episodes give hope that these differences would transform into a higher survival rate in a more extended follow-up period.

Our findings show that implementation of the vascular disease management program (invasive management of patients with ACS, new antithrombotic drugs, increased use of statins) significantly reduced total mortality and the rate of repeated coronary episodes at least within 12 months of follow-up in the comparison groups of patients. However, adverse shifts in the prevalence of key RFs in real-world clinical practice can offset the benefits of invasive methods and, thus, require additional efforts to be corrected.

Limitations

Different inclusion criteria and protocols of the ORACUL I and ORACUL II studies did not allow for a complete comparison of the used therapies and treatment compliance. The ratio of sizes of the groups compared did not allow matching the groups by all the different parameters without a significant decrease in the number of the observed cases, which forced us to select the most significant different parameters for the matching procedure.

Funding

The study was organized by the Central State Medical Academy at the Administrative Department of the President of the Russian Federation (previously Training and Research Center at the Administrative Department of the President of the Russian Federation). There were no external sources of financial support.

No conflict of interest is reported.

The article was received on 25/04/2020

REFERENCES

1. Zateyshchikov D.A., Volkova E.G., Guz I.O., Evdokimova M.A., Aseycheva O.Yu., Galyavich A.S. et al. Treatment of patients who underwent acute coronary syndrome, according to the Russian multicenter prospective observational study. Pharmateca. 2009;12 (186):109–13. [Russian: Затейщиков Д.А., Волкова Э.Г., Гузь И.О., Евдокимова М.А., Асейчева О.Ю., Галявич А.С., и др. Лечение больных, перенесших острый коронарный синдром, по данным российского проспективного многоцентрового наблюдательного исследования. Фарматека. 2009;12 (186):109–13]
2. Averkova A.O., Brazhnik V.A., Koroleva O.S., Zubova E.A., Hasanov N.R., Chichkov Yu.M. et al. Acute coronary syndrome in young patients with familial hyperchoolesterolemia based on the results of Oracul II observation trial. Medical news of the North Caucasus. 2017;12 (1):5–8. [Russian: Аверкова А.О., Бражник В.А., Королева О.С., Зубова Е.А., Хасанов Н.Р., Чичков Ю.М. и др. Особенности течения острого коронарного синдрома у молодых больных с гиперлипидемией по данным наблюдательного проекта ОРАКУЛ II. Медицинский вестник Северного Кавказа. 2017;12 (1):5–8]. DOI: 10.14300/mnnc.2017.12001
3. Ge Z, Baber U, Claessen BE, Farhan S, Chandrasekhar J, Li SX et al. The prevalence, predictors and outcomes of guideline-directed medical therapy in patients with acute myocardial infarction undergoing PCI, an analysis from the PROMETHEUS registry. Catheterization and Cardiovascular Interventions. 2019;93 (3):E112–9. DOI: 10.1002/ccd.27860
4. Choe JC, Cha KS, Ahn J, Park JS, Lee HW, Oh J-H et al. Comparison of prescription rates and clinical outcomes in acute coronary syndrome patients who underwent percutaneous coronary intervention using different P2Y12 inhibitors in a large observational study. International Journal of Cardiology. 2019;274:21–6. DOI: 10.1016/j.ijcard.2018.09.011
5. Biswas S, Andrianopoulos N, Papapostolou S, Noaman S, Duffy SJ, Lefkovits J et al. Does the subtype of acute coronary syndrome treated by percutaneous coronary intervention predict long-term clinical outcomes? European Heart Journal - Quality of Care and Clinical Outcomes. 2018;4 (4):318–27. DOI: 10.1093/ehjqcco/qcy009
6. Cirillo P, Di Serafino L, Patti G, Antonucci E, Calabrò P, Gresele P et al. Gender-Related Differences in Antiplatelet Therapy and Impact on 1-Year Clinical Outcome in Patients Presenting With ACS: The START ANTIPLATELET Registry. Angiology. 2019;70 (3):257–63. DOI: 10.1177/0003319718783866
7. D'Ascenzo F, Celentani D, Brustio A, Grosso A, Raposeiras-Roubín S, Abu-Assi E et al. Association of Beta-Blockers with Survival on Patients Presenting with ACS Treated with PCI: A Propen-

ISSN 0022-9040. Kardiologiia. 2020;60(9). DOI: 10.18087/cardio.2020.9.n1172

sity Score Analysis from the BleeMACS Registry. American Journal of Cardiovascular Drugs. 2018;18 (4):299–309. DOI: 10.1007/s40256-018-0273-4
8. Erlikh A.D. Twelve months outcomes in patients with acute coronary syndrome, by the national registry RECORD-3. Russian Journal of Cardiology. 2018;23 (3):23–30. [Russian: Эрлих А.Д. 12-месячные исходы у пациентов с острым коронарным синдромом, включенных в российский регистр «РЕКОРД-3». Российский кардиологический журнал. 2018;23 (3):23–30]. DOI: 10.15829/1560-4071-2018-3-23-30
9. Hamilos M, Petousis S, Xanthopoulou I, Goudevenos J, Kanakakis J, Sitafidis G et al. Antiplatelet treatment in diabetic patients with acute coronary syndrome undergoing percutaneous coronary intervention: a GReek AntiPlatElet registry substudy. Coronary Artery Disease. 2018;29 (1):53–9. DOI: 10.1097/MCA.0000000000000547
10. Panduranga P, Al-Rashidi M, Al-Hajri F. n-Hospital and One-Year Clinical Outcome of Percutaneous Coronary Intervention in a Tertiary Hospital in Oman: Oman PCI Registry. Oman Medical Journal. 2017;32 (1):54–61. DOI: 10.5001/omj.2017.10
11. Alhabib KF, Kinsara AJ, Alghamdi S, Al-Murayeh M, Hussein GA, Al-Saif S et al. The first survey of the Saudi Acute Myocardial Infarction Registry Program: Main results and long-term outcomes (STARS-1 Program). PLOS ONE. 2019;14 (5):e0216551. DOI: 10.1371/journal.pone.0216551
12. Minushkina L.O., Brazhnik V.A., Averkova A.O., Rogozhina A.A., Evdokimova M.A., Korolyova O.S. et al. Acute coronary syndrome in patients with diabetes mellitus: unified data of multicenter observational trials ORACLE I and ORACLE II. Therapy. 2019;5 (1):68–80. [Russian: Минушкина Л.О., Бражник В.А., Аверкова А.О., Рогожина А.А., Евдокимова М.А., Королева О.С. и др. Острый коронарный синдром у больных с сахарным диабетом: объединенные данные многоцентровых наблюдательных исследований ОРАКУЛ I и ОРАКУЛ II. Терапия. 2019:5 (1):68–80]