



## Original Article

# Comparison of the outcomes of the prolonged antianginal therapy use in stable coronary artery disease patients according to the data of randomized and observational studies

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## ABSTRACT

**Objective:** To compare the results of treatment with antianginal drug nicorandil in patients with stable coronary artery disease according to the results of the observational study (OS) «NIKEA» and randomized controlled trial (RCT) «IONA».

**Methods:** «NIKEA» observational program included 590 patients with stable angina pectoris. Subgroups in the OS were formed based on the adherence to nicorandil use. Adherence was assessed during follow-up direct questioning. «IONA» RCT included 5126 patients with stable angina pectoris.

**Results:** Follow-up period and mean age of patients were equal in OS and RCT. In OS the group of adherent to nicorandil use patients had fewer males, life-saving drugs were administered significantly more often than in RCT, comorbidities (arterial hypertension, peripheral atherosclerosis and diabetes mellitus) were more pronounced. Angina pectoris class III was diagnosed in 32% of the OS patients vs 11% of the RCT patients, and class I – in 4.4% and 26%, respectively ( $p < 0.001$ ). Both in RCT and OS, there were significantly fewer cases of all cardiovascular events in the groups of nicorandil and adherent to nicorandil use patients in comparison with the groups of placebo and nonadherent patients. Both in RCT and OS the use of nicorandil led to significant decrease in the risk of all cardiovascular events.

**Conclusion:** Results of the efficacy and effectiveness studies complement each other and give the opportunity to assess the realisation of the RCT results in real clinical practice.

## What's new

- results of the observational and randomized trials were compared
- adherence to nicorandil use was assessed
- outcomes of the prolonged use of nicorandil in stable coronary artery disease patients were assessed

## 1. Introduction

Medication therapy is currently the most common medical intervention in the treatment of most diseases, especially chronic non-communicable diseases, including stable coronary artery disease

(SCAD).

Results of the COURAGE and ISCHEMIA studies proved that the potential of pharmacotherapy in the effective treatment of SCAD patients remains very high [1,2]. This is also reflected in the clinical guidelines for the treatment of such patients [3]. Nevertheless, positive effect of most antianginal drugs on disease outcomes has not been proved. One of the exceptions is the potassium channel activator nicorandil that demonstrated a 14% reduction of cardiovascular events ( $p = 0.027$ ) in SCAD patients according to the results of the randomized controlled trial (RCT) «IONA» [4].

On the other hand, there is evidence that in real clinical practice (RCP) efficiency of medications proved by the results of RCT was less

**Abbreviations:** ACS, acute coronary syndrome; DOAC, direct oral anticoagulants; CABG, coronary arterial bypass grafting; HR, hazard ratio; MI, myocardial infarction; NHS, Nurses' Health Study; OS, observational studies; PCEP, primary combined endpoint; PCI, percutaneous coronary intervention; RCP, real clinical practice; RCT, randomized controlled trial; SCAD, stable coronary artery disease.

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pronounced and convincing [5,6]. This can be explained by the difference of conditions and characteristics of different study designs – RCT and observational studies (OS), for example, strict inclusion and exclusion criteria, which usually limit participation in RCT of some patient categories (elderly, patients with severe comorbidities, multicomponent concomitant therapy, etc) [7–9]. Because of this, two terms were introduced – efficacy and effectiveness – meaning effectiveness of a medication in the ideal conditions of RCT and in the conditions of RCP, respectively [6,10].

Since the beginning of the 21 century, comparative studies on assessment of reproducibility of the results of RCT under the conditions of RCP and testing of hypothesis formulated based on the results of OS under strict conditions of RCT have become increasingly widespread.

The aim of this study was a comparative assessment of the results of treatment of patients with SCAD using nicorandil according to the results of the RCT «IONA» [4] and OS «NIKEA» [11].

## 2. Materials and methods

### 2.1. Observational program «NIKEA»

«NIKEA» is a prospective cohort study conducted from July 07, 2013 to December 13, 2017 in 14 medical centers of 13 regions of the Russian Federation (Fig. 1).

«NIKEA» observational program included 590 patients (329 (55.8%) males) with SCAD, angina pectoris. The mean age of the patients was  $65.1 \pm 9.6$  years, and the mean follow-up time was  $1.8 \pm 0.4$  years. In addition to standard anti-ischemic therapy, all patients were recommended the use of nicorandil at a dose of 20 mg per day, which was titrated during in-person visits up to 40 mg per day.

The program included 3 in-person visits: inclusion (V0), 1 and 3 months (V1 and V3, respectively), and phone contacts – 9, 15, and 21 months after V0. During the last phone contact – follow-up (FU) – outcomes were evaluated. Components of the primary combined endpoint

(PCEP) were all-cause death, new cases of non-fatal acute myocardial infarction (MI), stroke, emergency hospitalisation due to decompensation of chronic heart failure, atrial fibrillation, and CAD.

FU with patients or their relatives was performed in 524 cases: 509 patients were alive, and 15 had died. Subgroups in OS were formed depending on patients' adherence to nicorandil use, which was assessed during FU using indirect method of assessment of adherence – direct doctors' questioning [12,13]. Those patients who had been taking the medication prior to the phone contact (FU 21 months) were considered adherent to nicorandil use, those who had not been taking nicorandil by the time of FU were considered nonadherent. Adherence was assessed in 479 patients: 242 were adherent to nicorandil (123 (50.8%) males), and 237 (137 (57.8%) males) were nonadherent.

All patients of the «NIKEA» study signed the informed consent form.

Protocol and all the documents of the study have been approved by the Local independent ethics committee.

Observational study «NIKEA» was conducted with the support from OAO «PIC-FARMA» which affected neither the results of the study, nor their interpretation and the findings of the research.

### 2.2. Randomized controlled trial «IONA»

Material and some of the results of the RCT «IONA» were taken from the publication in the Lancet Journal [4].

This RCT included 5126 patients with stable angina pectoris class I-IV: 2561 patients took nicorandil (1962 (75%) males), and 2565 patients received placebo. Mean age of patients was  $67.0 \pm 8.0$  years; and mean follow-up time was  $1.6 \pm 0.5$  years. Starting dose of nicorandil 20 mg per day was later titrated up to 40 mg per day provided that it was tolerated well and lacked side effects [14].

Components of the PCEP of the «NIKEA» study mostly accorded to the additional outcomes of the RCT «IONA» named all cardiovascular events, which included cardiovascular death, non-fatal acute MI and stroke, emergency hospitalisation due acute coronary syndrome (ACS),

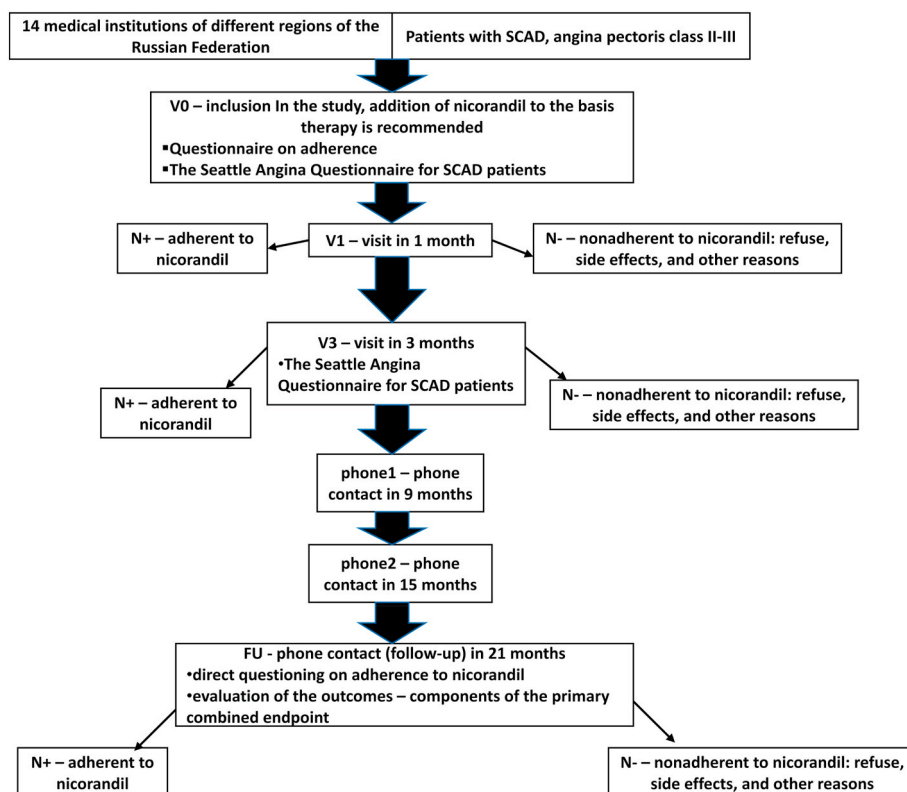


Fig. 1. Diagram of the «NIKEA» observational study.

and transient ischemic attack.

### 2.3. Statistical analysis

Statistical program package SPSS Statistics 23.0 (IBM, USA) was used for statistical analysis. Descriptive statistics was presented as means and standard deviations for quantitative variables with normal distribution and as medians and interquartile range for non-normal distribution (normality of distribution was determined using the Shapiro-Wilks W criteria). Qualitative variables were described using proportions in percentage. Differences between independent factors from the «IONA» and «NIKEA » studies were assessed using Student's t-test, Mann-Whitney U test, Fisher's exact test, or Chi-square test with Yates's correction for continuity.

For the assessment of the considered outcomes and comparative analysis of the results of RCT and OS, Kaplan-Meier survival method, log-rank test and Cox proportional hazards model were used.

Differences were considered statistically significant if the p-value was less than 0.05.

### 3. Results

RCT and OS included patients with SCAD, angina pectoris, practically of the same age. The IONA study included more males, 76.0% versus 55.8%, which probably was due to targeted selection and non-consequential inclusion of patients into RCT. Follow-up period was equal in RCT and OS:  $1.6 \pm 0.5$  years and  $1.8 \pm 0.4$  years, respectively.

Data on concomitant pathology of patients of compared studies are presented in Table 1. OS patients had more distinctive comorbidity (more cases of diabetes mellitus, peripheral atherosclerosis, arterial hypertension) than RCT patients. It should be mentioned that RCT patients in comparison with OS patients more often had a history of coronary arterial bypass grafting (CABG) — 22% versus 9%, but less often — percutaneous coronary intervention (PCI) — 14% versus 21%, which may indicate the change of intervention procedures in the treatment of SCAD from surgery to mini-invasive procedure.

Comparison of the severity of angina pectoris revealed that angina

**Table 1**  
Comparison of the initial characteristics of RCT and OS patients.

Data of the studies	IONA	NIKEA (initially)	p
	Nicorandil subgroup (n = 2565)	Total (n = 590)	
<b>Categorical risk factors</b>			
Male	1962 (76%)	329 (55.8%)	<0.001
Diabetic	197 (8%)	128 (21.7%)	<0.001
Hypertensive	1197 (47%)	564 (95.6%)	<0.001
Current smoker	417 (16%)	87 (14.7%)	0.4
<b>History of vascular disease</b>			
Previous MI	1696 (66%)	374 (63.4%)	0.2
Previous stroke	134 (5%)	22 (3.7%)	0.2
Previous PCI	360 (14%)	125 (21.2%)	<0.001
Previous CABG	572 (22%)	54 (9.2%)	<0.001
History of peripheral vascular disease	289 (11%)	175 (29.7%)	<0.001
<b>CCSF classification for angina</b>			
I, n (%)	671 (26%)	26 (4.4%)	<0.001
II, n (%)	1605 (63%)	375 (63.6%)	0.7
III, n (%)	272 (11%)	189 (32.0%)	<0.001
IV, n (%)	17 (<1%)	1 (0%)	0.1
<b>Other data, mean <math>\pm</math> SD</b>			
Age, years	$67.0 \pm 8.0$	$65.1 \pm 9.6$	>0.05
Follow-up time, years	$1.6 \pm 0.5$	$1.8 \pm 0.4$	>0.05
<b>Drug therapy (life-saving drugs)</b>			
Beta-blockers	1453 (57%)	519 (88.0%)	<0.001
ACE inhibitors	739 (29%)	544 (92.2%)	<0.001
Aspirin/antiplatelets	1197 (47%)	547 (92.7%)	<0.001
Statins	1449 (56%)	538 (91.2%)	<0.001

class II occurred in RCT and OS patients in similar percent of cases (63% and 63.6%), OS had 6 times less patients with angina class I (4.4% versus 26%) and 3 times more patients with angina class III (32% versus 11%) in comparison with RCT. There were no cases of severe angina (class IV) in OS and only 17 patients (less than 1%) in RCT (Table 1).

Analysis of medical therapy of SCAD to which nicorandil was added revealed that drugs with evidence-based positive influence on SCAD outcomes (life-saving drugs) were significantly more often ( $p < 0.0001$ ) prescribed in the «NIKEA » study (Table 1).

Survival analysis with the use of the Kaplan-Meier survival curves and long-rank test demonstrated significantly less number of all cardiovascular events in RCT and PCEP in OS in groups of nicorandil-taking patients ( $p = 0.027$  and  $p = 0.03$ ) (Fig. 2).

Hazard ratio (HR) of all cardiovascular events, non-fatal acute MI, and stroke in nicorandil/placebo and adherent/nonadherent to nicorandil use groups is presented in Table 2. It can be noticed, that both in RCT and OS, nicorandil use led to more pronounced decrease of HR of all cardiovascular events (or cases of PCEP) despite the differences in the events or individual components of PCEP did not reach the statistically significant level (Table 2).

Application of the Cox regression analysis revealed that the use of nicorandil, antiplatelet drugs, beta-blockers and ACE inhibitors or ARB reduced the HR of the PCEP components development approximately by 50%, but only nicorandil use was a statistically significant factor in this result: HR = 0,41 CI95% [0,17; 0,97],  $p = 0,042$  (Fig. 3).

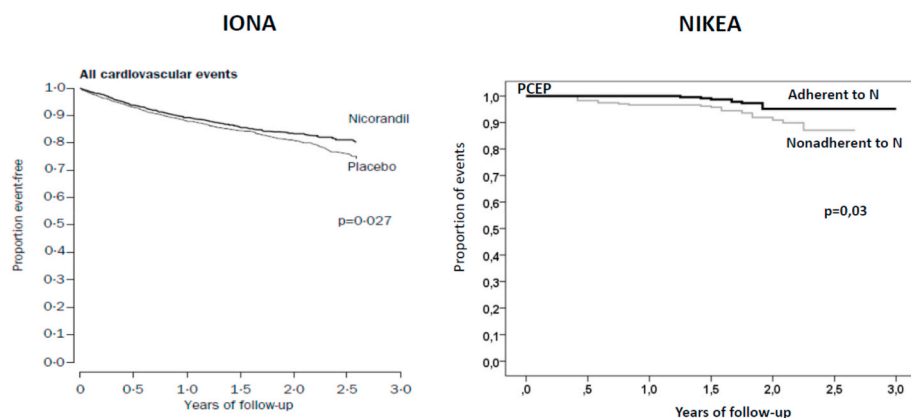
### 4. Discussion

Comparison of the results of RCT and OS conducted with the 20-years age difference allow not only the assessment of the effectiveness of the antianginal drug nicorandil in the ideal conditions of the RCT and in RCP (efficacy & effectiveness) but also observe the changes in the main tendencies of the course of SCAD and treatment of such patients.

The descriptive analysis of the initial data of the RCT « IONA» and OS « NIKEA » revealed that in the conditions of the RCP (according to the OS data), there were practically no cases of severe angina pectoris, class IV, which was probably due to wider implementation of interventional methods of treatment of SCAD, including PCI, and more frequent use of anti-ischemic drugs. On the other hand, generally patients in the OS were in worse condition than those included in the RCT: they more often had angina pectoris class III (in RCT patients – class I), also they had more pronounced comorbidity, which was probably due to exclusion of patients with multiple severe comorbidity from RCT.

Although RCT is the golden standard of the evidence-based medicine and possibility and necessity of the use of the results of observational studies in the development of clinical guidelines is still discussed and questioned by some authors, studies of both designs have their strong and weak sides. The main disadvantage of the RCT is the ideal conditions that differ from the usual clinical practice – the so called unsatisfactory exterior validity along with a high interior validity [7,9]. Thus, in the work of Travers J et al., it was revealed that all inclusion in at least one RCT criteria that lay in the basis of clinical guidelines were found only in 4% of bronchial asthma patients of general sample [9]. Comparison of the RCT and OS recruiting patients with diabetes mellitus type 2 showed that patients in OS had more severe course of the disease with higher levels of glycated hemoglobin and more severe comorbidity [6]. Oncological patients in RCP were older than RCT participants and had worse outcomes. More than half of the cardiological patients in OS did not meet the inclusion criteria in the corresponding RCT criteria [7]. Similar results were also demonstrated in this descriptive analysis of patients with SCAD that took part both in RCT and in OS.

On the contrary, in comparison with RCT conditions, OS conditions are maximally close to the RCP – high exterior validity, but due to lack of randomisation and many confounding factors, and also possible bias, results of the OS should be interpreted with caution [15]. Realisation of the hypothesis that were formulated based on the results of OS in the

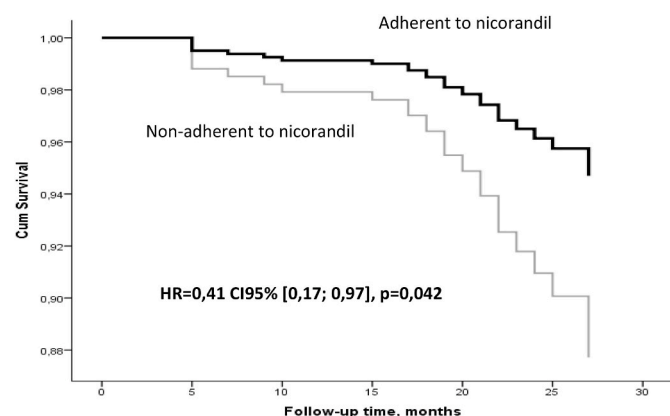


**Fig. 2.** Kaplan-Mayer curves and significance of differences according to log-rank criteria in «IONA» и «NIKEA» studies. Kaplan-Mayer curves, log-rank criteria, N–nicorandil, PCEP-the primary combined endpoint (Figure of Kaplan-Meier curves from the IONA study is reprinted from The Lancet, Vol. number 359, Author(s): The IONA Study Group, Title of article « Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomized trial», Pages No. 1269–1275, Copyright (Year) 2002, with permission from Elsevier).

**Table 2**

Comparison of outcomes in the groups of nicorandil/placebo and adherent to nicorandil/nonadherent to nicorandil patients according to the results of RCT and OS.

	IONA	p, Nicorandil (2565)/ Placebo (2561)	NIKEA	p, Adherent to nicorandil (242)/ Nonadherent to nicorandil (237)
All cardiovascular events	HR = 0,86 CI95% (0,75; 0,98)	p = 0,027	HR = 0,21 CI95% (0,10; 0,48)	p<0,0001
Non-fatal myocardial infarction	HR = 0,76 CI95% (0,54; 1,08)	p = 0,17	HR = 0,32 CI95% (0,07; 1,61)	p = 0,17
Nonfatal stroke	HR = 0,92 CI95% (0,59; 1,45)	p = 0,8	HR = 0,20 CI95% (0,02; 1,66)	p=0,12



**Fig. 3.** Cox regression analysis for stratum of adherent/nonadherent to nicorandil use patients of the «NIKEA» study.

results of the subsequent RCT was even more unsatisfactory. According to V. Tai et al. who analyzed the reproducibility of the results of Nurses’ Health Study (NHS) within some RCT, very low consistency was revealed [16].

Nevertheless, OS helps to clarify how data from RCT on effectiveness and safety of drugs are realized in clinical practice. Thus, for example, it

was found that effectiveness of direct oral anticoagulants (DOAC) in prevention of stroke, according to RCT, exceeded warfarin and in conditions of RCP was true only for new users of DOAC, but not for patients who have previously taken warfarin [5,17].

In all probability, results of RCT and OS complement each other. Therefore, for the development of clinical guidelines and assessment of effectiveness and safety of one or another method of treatment, all available information on this issue should be considered. Although in the «NIKEA» study, all the limitations of the OS were present, these results allowed to receive additional information on the effectiveness of prolonged nicorandil use within RCP in SCAD patients and demonstrate real influence of the medication on disease outcomes.

**5. Conclusion**

Results of the efficacy and effectiveness studies complement each other and give the opportunity to assess the realisation of the RCT results in RCP.

**Prior posting and presentations**

This article has not been published previously. It contains original unpublished work and is not being submitted for publication elsewhere at the same time. Its publication is approved by all authors.

**Declaration of competing interest**

Observational study «NIKEA» was conducted with the support from the Russian pharmaceutical company «PIC-PHARMA» which affected neither the results of the study, nor their interpretation and the findings of the research.

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**Appendix A. Supplementary data**

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.conctc.2021.100743>.

**Authors’ contributions**

Martsevich S.Yu.: substantial contributions to conception and design; revising the article critically for important intellectual content; final approval of the version to be published.

Lukina Yu.V.: analysis and interpretation of data; drafting the article.

Kutishenko N.P.: substantial contributions to conception and design; revising the article critically for important intellectual content.

Semenova Yu.V.: drafting the article.

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