The Russian multicenter observational study of ACS patients with at least one-year follow-up -the ORACLE (ObseRvation after Acute Coronary syndrome for deveLopment of trEatment options) study

Protocol
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TABLE OF CONTENT

SUPPLEMENT

ABBREVIATIONS

ACS Acute Coronary Syndrome
AS acute stroke
CABG Coronary artery bypass grafting
CRF Case report form
CAG coronary angiography
CHD – coronary heart disease
CPK Creatine phosphokinase
CPK-MB Creatine phosphokinase-MB
ECG electrocardiogram
MI Myocardial Infarction
PCI Percutaneous Coronary Intervention
TIA transitory ischemic attack
Tn troponin
UA unstable angina

Introduction

The role of genetic factors in the development of CHD exacerbations studied not enough. Most research in this area planned and carried out on a "case-control". Using a similar protocol entails significant errors are associated with a high incidence of subclinical atherosclerotic vascular lesions. Moreover, much of atheroma is extravasal, making it impossible to identify them by angiography. Therefore, necessary to conduct prospective studies to estimate the frequency of so-called hard endpoints. Previously, similar trials were conducted, mainly in connect with drug approving procedures. The spread data from them to other patients directly is not entirely justified. At the same time, the influence of genetic factors in this group of patients can be substantial.

In the previous part of the study, the sample of patients of Moscow, St. Petersburg, Kazan, Chelyabinsk, Stavropol, Perm, and Rostov-on-the-Don was formed, of 1,200 people admitted due to acute coronary syndrome (ACS) including unstable angina and acute myocardial infarction, at coronary care units with follow-up for three years. We found several factors, including genetic, that significantly affect the outcomes of the disease. Coronary atherosclerosis and its complications now considered as a multifactorial disease associated with inherent factors. Therefore, the project provides, besides accounting a significant amount of clinical and instrumental data, the determination of a wide range of genotypes and alleles of polymorphic markers candidate genes encoding the protein factors of the hemostatic system, enzymes of lipid metabolism system, and anti-inflammatory cytokines. It is assumed that the prediction outcomes of coronary heart disease should be carried out taking into account the fact that several factors (gender, diabetes, age, aortic stenosis, atrial fibrillation, etc.) can not only significantly change the forecast itself but also affecting the significance of other risk factors. Since the last study, the standards significantly of ACS management changed. Invasive treatment not only creates opportunities to reduce coronary mortality but also increased demands on the patient's adherence to the assigned medication and creates additional risks associated with its activity (especially with an antithrombotic treatment activity). In these circumstances, the development of personalized approaches to prescribing drugs is particularly important. Thus, the prediction of coronary heart disease outcomes after an ACS on a set of clinical, instrumental, biochemical and genetic indicators is of great importance, as it allows to plan the most optimal treatment for the individual patient.

1. THE AIM OF THE STUDY

To develop a model of individualized risk of coronary heart disease outcomes and side effects of therapy based on clinical and instrumental, biochemical, and genetic parameters in patients with ACS.

2. STUDY DESIGN AND PATIENT'S SELECTION

2.1. STUDY DESIGN

This is the Russian multicenter observational study of ACS patients with at least one-year follow-up. We planned to include 1700 ACS patients admitted to invasive hospitals. The follow-up will continue until at least 200 deaths for any reason.

2.2. INCLUSION CRITERIA

- ACS patients with indications for PCI hospitalization, regardless of whether or not carried out PCI.
- Signed informed consent to participate in the study.

2.2.1. INCLUSION CRITERIA FOR ACS PATIENTS WITHOUT SEGMENT ST ELEVATION

- All patients meet the criteria of very high, high, or intermediate risk and selected low-risk patients according to current guidelines.

1.1.1. THE INCLUSION CRITERIA FOR PATIENTS WITH ACUTE CORONARY SYNDROME WITH ST ELEVATION OR ALREADY FORMED LARGE MYOCARDIAL INFARCTION

Patients who have been hospitalized with symptoms caused by acute myocardial (heart attack prescription no more than 10 days, hospitalization time) and at least one of the following additional criteria identified at admission:

- elevation ST: ST persistent increase 1 mm in two contiguous leads limb or ST rise to 2 mm in two adjacent precordial leads
- the emergence of a new blockade of left bunch branch block
- dynamics of acute myocardial infarction (appearance of pathological Q, reduction of R, change the final portion of the ventricular complex)

1.2. EXCLUSIONARY CRITERIA

- The lack of patient consent for participation in the study
- Inability to contact with the patient after discharge

2. TREATMENT

All patients should receive the standard treatment for acute coronary syndrome and related diseases according to the current guidelines.

3. STUDY PROCEDURES

3.1. THE SEQUENCE OF STUDY

Stationary Phase

1st day:

Symptoms of acute coronary syndrome, leading the patient to the hospital
Conformity assessment criteria for inclusion in the study

Written informed consent
blood samples for genetic analysis
Filling Case Report Form (CRF)
2nd - 5th day
Filling in the missing information in the CRF
During the CAG or PCI is an extensive video research and filled with a separate PCI card
Upon cancellation of the CAG and PCI card is filled with the count of " rejection reason "
Register endpoint - filling in the relevant sections of the CRF
discharge planning
6th day - discharge from the hospital
Echocardiography - attached full movie, and is filled with a special card echocardiogram
Final inspection and afterfilling CRF
Talk with the patient follow-up plan
The introduction of information into an electronic database
Sending information to the Coordination Center for Research

Outpatient treatment stage

25 ± 5 days from the date of inclusion (but no earlier than 5 days after discharge)
Telephone contact with the patient or his relatives
Register endpoint and adherence to treatment - filling in the relevant sections of the CRF
90 ± 15 days from the date of inclusion
Telephone contact with the patient or his relatives
Register endpoint and adherence to treatment - filling in the relevant sections of the CRF
180 ± 15 days from the date of inclusion
control monitoring visit
ECG
Register endpoint and adherence to treatment - filling in the relevant sections of the CRF.
365 ± 15 days from the date of inclusion
Telephone contact with the patient or his relatives.
Register endpoint and adherence to treatment - filling in the relevant sections of the CRF
Next phone contacts 1 time in 6 months to achieve thereof, the observation of the last patient included in the study (or up to 200 deaths, if for the planned observation period their number was less).
The final filling of card and electronic form, sending the information to the coordination center.
Appropriate CRFs and forms for the events should be completed in accordance with the instructions in the manual of the researcher.

In the case report of the patient information is recorded on the adverse clinical outcomes that have developed since the last contact with the patient (see. the relevant section of the CRF). Also recorded group of drugs, which the patient took over this time period.

4. ENDPOINTS

4.1. The primary endpoint

- Dearth from any causes

5.2. Secondary end-points

1. cardiovascular (atherothrombotic) events
(cardiovascular death, non-fatal myocardial infarction, non-fatal stroke)
2. non-fatal myocardial infarction
3. recurrent acute coronary syndrome (all cases of recurrent myocardial infarction or unstable angina after the index events)
4. recurrent PCI
(all cases of recurrent PCI after the index hospitalization)
5. complicated atherosclerosis
6. non-fatal stroke

5.3 Other Pre-specified Outcome Measures:

1. Bleeding
all cases of bleeding during and after the index hospitalization

6.3. Defining endpoints

6.3.1. Acute myocardial infarction

any two of the following criteria meets the diagnosis of acute, evolving or recent myocardial infarction:
typical dynamics of biochemical markers of myocardial necrosis to a value above the upper limit of normal two (or if the markers have increased by more than 50% of the minimum level of detection of the enzyme) and at least one of the following:

a) symptoms of ischemia
b) The appearance of pathological Q wave on ECG
c) ECG changes indicating ischemia (increase or decrease of ST segment)
d) Coronary intervention or pathological evidence for acute myocardial infarction

4.1.1. <u>Previous myocardial infarction</u>

The emergence of new wave Q on an electrocardiogram (ECG compared to the previous visit), the appearance of new zones in the a- or dyskinesia echocardiogram.
Documented in another hospital myocardial infarction.

4.1.2. <u>Unstable angina</u>

It is defined as a recurrent chest pain / symptoms of ischemia, continuing for more than 5 minutes, with documented typical ECG changes indicative

of ischemia and / or improving cardiac enzymes and markers of myocardial damage and require hospitalization.

4.1.3. Fatal case

All cases of death will be merged the concept of "total mortality" and will be divided according to the genesis of "due to cardiovascular disease" and "not associated with cardiovascular disease," according to information provided to the physician-researcher. Fatal, "due to cardiovascular disease," it will be divided according to the genesis of "cardiovascular mortality" and mortality from "other cardiovascular disease." Death as a result of acute myocardial infarction, CABG, sudden cardiac death will be classified as "cardiovascular mortality." The category of death from other cardiovascular diseases will be charged any additional cases related to the cardiovascular system (ie, death from stroke, major bleeding, pulmonary embolism, as a result of the operation). For the category "non-cardiovascular disease deaths' are referred all cases of clearly non-cardiac origin (eg, death from cancer, injuries, infections, etc.).

4.1.4. Stroke, TIA

is defined as the presence of a new focal neurologic disorder considered vascular in origin, with signs or symptoms continued more than 24 hours. Stroke is classified as ischemic, haemorrhagic or indeterminate type.

4.1.5. Complicated peripheral arterial disease

Cases atherosclerosis peripheral arteries leading to the need for surgery (reconstructive vascular surgery, amputation, carotid endarterectomy, aorto-femoral bypass, etc.)

4.1.6. Coronary revascularization

Taking into account all the cases of revascularization procedures

5. COLLECTION AND ANALYSIS OF STATISTICAL DATA.

Statistical analysis was performed using a standard statistical package IBM SPSS Statistics Version 22 for Windows and MedCalc software version 18.3. It involves analysis of clinical predictors

- all cause mortality

- cardiovascular mortality

- all cardiovascular events

- stroke

- any, significant and major hemorrhage

For continuous variables will be analyzed and the distribution criteria for its compliance with the normal using the Kolmogorov-Smirnov test. To describe the features of the normal distribution using the mean with standard deviation

indication (M ± SD). For signs with non-normal distribution when reporting the results indicate the median and interquartile range - the 25th and 75th percentiles (Me (Q1-Q3)). Discrete values are calculated as a percentage, the significance of differences were compared by Pearson criterion $\chi 2$. Comparison of quantitative traits obeying the normal distribution, is carried out using t-criterion Student, unormal distribution - by using the non-parametric test, the Mann - Whitney and Kruskal - Wallis test for unrelated groups. For quantitative evaluation of the values calculated correlation coefficient is obtained and the accuracy depending on the Pearson's criteria (normal distribution) or Spearman (with a deviation from the normal distribution) for bilateral hypothesis testing criterion. The rating values of the predictor is conducted by plotting ROC curve and calculating the area under the curve (AUC). Treatment Evaluation of Frequency Allocations alleys and genotypes studied these genes will be performed using "Gene Expert" unified program. Genotype frequency distribution was calculated (the Hardy-Weinberg equilibrium test), genetic risk of NO using multiplicative general, dominant and recessive inheritance models. To assess the effect of clinical factors on the independence of the risk of adverse outcomes is performed using the Kaplan-Meier method using the log-rank test (Log Rank) and using Cox regression.

The regression analysis Univariate Cox included parameters are different when the comparative analysis between the groups of patients with a favorable and unfavorable outcome. The development of prognostic functions performed by using multivariate logistic regression. For all types of analysis were considered statistically significant value of $p < 0,05$.

It is supposed to analyze the prognostic data for specific groups of patients:

- patients 75 years and older

- patients with "early" debut atherosclerosis (men younger than 55 years, women younger than 60 years)

- patients with diabetes

- patients with CKD

7. ETHICAL AND LEGAL ASPECTS.

7.1 Informed consent of the patient.

Patients who meet all eligibility criteria, are considered suitable. Before inclusion in the clinical study of the patient must provide written consent to participate in the study, after the nature of the study will be explained verbally and in writing. Patients should be informed that in the course of study they will have taken blood for research purposes, including for genetic analysis.

7.2 The principle of confidentiality.

The data obtained from the study, and stored in the computer must be protected, as required by the law on personal data protection. The researchers will treat all personal information about the patient obtained during the investigation, in full respect of medical confidentiality and personal data protection law.

8. DATA OWNERSHIP AND USE OF RESEARCH RESULTS.

Each research group has the right to publish their own data, obtained as a result of the study.

Publication and other use of materials produced in other centers, with the consent of researchers, guiding the work of the centers.