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Observational Prospective study to esTIMAte the rates of outcomes in patients undergoing PCI with drug eluting stent (DES) implantation who take statins – follow-up (OPTIMA II)

Study dates:	**First Subject In: 28/05/2014**
	Last Subject Last Visit: 29/05/2015

NIS REPORT SYNOPSIS

Observational Prospective study to esTIMAte the rates of outcomes in patients undergoing PCI with drug eluting stent (DES) implantation who take statins – follow-up (OPTIMA II)

The current follow-up study was conducted to reveal the rates of Major Adverse Cardiovascular and Cerebrovascular Events (MACCE) during 4-year follow-up in patients participated in OPTIMA study.

Study centre(s). One site participated in the study - the Russian Cardiology Research and Production Complex

Publications. None

Objectives.

Primary objective

Primary objective of this study was to estimate the rates of Major Adverse Cardiovascular and Cerebrovascular Events (MACCE) in patients after drug-eluting stents (DES) implantation who took statins at baseline after 4 years PCI.

Secondary objectives

Secondary objectives of the study were:

1. To evaluate proportion of patients who took statins 4 years after PCI with DES implantation and who discontinued statin therapy;
2. To evaluate proportion of patients who achieved target level of Low Density Lipoprotein Cholesterol (LDL-C) less 1,8 mmol/l;
3. To evaluate level of LDL-C, lipoprotein A, inflammatory markers, 4 years after PCI for Major Adverse Cardiovascular and Cerebrovascular Events (MACCE);
4. To estimate adherence to the therapy with statins according to questionnaire;
5. To evaluate proportion of patients who discontinued statin therapy, beta-blockers and ACE inhibitors therapy and identify their characteristics;
6. To estimate Seattle angina questionnaire (SAQ) score 4 years after PCI.

Study design

This project was 3-years follow-up of OPTIMA study. This was an observational retro-prospective study based on the data collected during one visit: 4-year after PCI performed at the Russian Cardiology Research and Production Complex. From the date of the study start and until the end of the study investigators enrolled patients participated in OPTIMA study. Only patients, who consented

to participate in the study and signed the informed consent form after being informed by a physician on the objectives and methods of the study, were enrolled into this project.

Changes to the protocol.

Protocol Amendment # 1 issued 27 May 2014 was aimed to include died patients to the analysis of major cardiovascular events in order to avoid systematic errors and risk findings in the study data.

Protocol Amendment # 2 issued 25 March 2015 extended the patients' enrolment period from Q1 2014 – Q1 2015 to Q1 2014 – Q2 2015. Sections "Safety Assessment" and "Training of study site personnel" were updated.

Target patient population and sample size.

The study population consisted of OPTIMA study patients who had not been lost for follow-up and had given a written informed consent. It was planned that 80-90% of patients participated in OPTIMA study would be enrolled into current project.

Inclusion criteria

The investigator had to review all inclusion and exclusion criteria prior to the study visit. The patient population observed in the study had to fulfil all of the following criteria:

- Participation in OPTIMA study (NIS-CRU-CRE-2009/1);
- Written informed consent provided prior the start of follow-up in the study.

Died patient might be enrolled into this observational study, but the access to his/her personal information and medical records was not allowed for the Sponsor/CRAs and source data validation (SDV) was not performed for this patient. The investigator identified the patient's data by unique number in OPTIMA study and provided the sponsor with the depersonalized medical information for statistical analysis.

Exclusion criteria

- Lost to follow-up patients of OPTIMA study;
- Subjects who were unwilling or unable to provide informed consent.

Criteria for evaluation (main variables).

No special procedures or examinations were performed in this study. The main point of this project was data collection using the patient medical records, as well as data collected by a physician during patient routine examination. All the procedures were standard; they were used in routine clinical practice for patients with stable angina after PCI.

The following variables were measured in this study:

- Demographic patient characteristics: age, gender;
- Relevant medical history:

  - CVD history (date of CAD diagnosis, previous coronary revascularizations (e.g. PCI or CABG) and their dates, history of myocardial infarction, history of atrial fibrillation, history of transient ischemic cerebral attack or stroke);
  - History of atherosclerosis: localization (cerebral atherosclerosis, atherosclerosis of lower extremities and other localizations), hypercholesterolemia duration, lipid-lowering therapy received by patient after PCI (medications, daily doses, duration of therapy, reason for discontinuation).

- Major adverse cardiac and cerebrovascular events (MACCE) composite of cardiac death, stroke, myocardial infarction and repeat target lesion revascularization after PCI;
- Current diagnosis of CAD (Stable Angina Pectoris severity (e.g. class I-II or class III-IV), CHF functional class (NYHA), etc.
- Significant concomitant diseases (diabetes mellitus, obesity, metabolic syndrome, peptic ulcer, muscle diseases, kidney and liver impairment, etc.).
- Current concomitant therapy: the trade names of medications, daily doses, route of administration, duration of therapy. Previous (after PCI) therapy with ACE inhibitors and beta-blockers with their daily doses, route of administration, duration of therapy and reasons for discontinuation.
- Physical examination data (body weight, height, waist circumference, systolic and diastolic blood pressure, heart rate, heart rhythm regularity).
- Laboratory tests results (LDL-C, C-reactive protein, leukocytes).
- ECG data.
- Assessment of adherence to the therapy with statins according to questionnaire.
- Seattle angina questionnaire (SAQ) score.

Results.

<u>Disposition of patients and baseline characteristics of study population</u>.

- 543 patients were enrolled in OPTIMA II study, i.e. 90.2% of patients participated in OPTIMA study (Follow-up analysis set). MACCE Follow-up analysis set included also data of 29 died patients and consists of 572 patients (95.0% of patients participated in OPTIMA study).
- The vast majority of patients (80.5%) were male, the mean age of study population was 64.75 (±9.334) years.
- The study patients had stable coronary artery disease; the mean disease duration (at date of enrolment in OPTIMA II study) was 7.09 (± 2.217) years. The majority of patients (61.6%) had no clinical signs of angina, 25.1% patients had stable angina of I – II functional class, 13.3% patients - III – IV functional class.
- According to Seattle angina questionnaire most of patients participated in OPTIMA II study had minimal angina manifestations: physical limitation was reported as minimal (median score was 88.83), anginal symptoms were unchanged over the preceding month (median score was 50.00), patients rated their angina frequency as minimal, i.e. they had angina less than once a week or

not at all (median score was 100.00), patients were satisfied with their treatment (median score was 81.25) and rated their quality of life as good (median score was 67.50).

- The vast majority of patients (93.4%) had no signs of chronic heart failure; chronic heart failure of I functional class was found in 4.4% patients, II functional class – in 1.9% patients, III functional class – only in 0.2% patients.
- Extracardial atherosclerosis was reported in the majority of patients enrolled in OPTIMA II study: cerebral atherosclerosis was found in 82.5% patients, atherosclerosis of the lower extremities - in 49.1% patients (intermittent claudication was reported in 7.1% patients of FU Analysis Set), atherosclerosis of other localization - in 8.7% patients.
- The most frequent other concomitant diseases were arterial hypertension reported in 82.2% patients, obesity – in 35.9% patients, metabolic syndrome – in 18.2% patients and diabetes mellitus diagnosed in 14.1% patients.
- The results of physical examination showed that the majority of patients enrolled in OPTIMA II study were overweight (mean BMI was 29.490 (± 3.9515), had normal blood pressure (mean values 130/80 mmHg) and regular pulse with median rest heart rate of 64 beats per minute.
- The results of laboratory tests demonstrated that level of LDL-C and examined inflammatory markers in the majority of patients participated in OPTUMA II study were within normal ranges: median of LDL-C level was 2.80 mmol/l, CRP - 0.165 mg/dl, leukocytes - 6.80 x 109 /l).

Therapy.

- At the time of enrolment in OPTIMA II study (mean time 4.42 ± 0.583 years after PCI) only 75.5% of patients received statins at baseline (during PCI) were treated with at least one statin. The most frequently administered medications were atorvastatin – in 52.1% patients, rosuvastatin – in 16.4% patients and simvastatin – in 5.7% patients. Pravastatin was administered to 5 patients, fluvastatin - to 1 patient.
- During follow-up period after Visit 2 of OPTIMA study (in the period between discharge from the hospital after PCI (4.42 ± 0.583 years after PCI) almost a quarter of patients (24.3%) cancelled statin therapy.
- At the time of enrolment (mean time 4.42 ±0.583 years after PCI) achievement of target level of LDL-C < 1,8 mmol/l was reported only for 7.7% of patients.
- Results of evaluating of adherence to lipid-lowering therapy with statins using a questionnaire showed the following: the majority of patients believed that they took prescribed tablets every day (87.2%), didn't stop taking prescribed tablets when his/her cholesterol level returned to normal (75.0%), didn't forget to take his/her cholesterol-lowering tablets (59.0%) or forgot to take them rarely - once a month or less (70.8%), believed that is it possible to miss a tablet without affecting his /her cholesterol levels once a month or less (75.8%).
- 76,6% of patients enrolled in OPTIMA II study (mean time 4.42 ±0.583 years after PCI) took any concomitant mediations apart from lipid-lowering therapy. Antiplatelets were received by 72.56% of study patients, selective beta blockers - by 58.56% of patients, ACE inhibitors - by 39.23% of patients, dihydropyridine derivates – by 22.28% of patients. Angiotensin II antagonists were taken only by 11,97% of study patients.

Major adverse cardiac and cerebrovascular events (MACCE).

- During follow-up period after PCI (4,42 ±0.583 years) 194 cases of MACCE were registered in 176 patients participated in OPTIMA II study (including data of died patients), most of them (159 patients) had only one MACCE.
- The incidence of MACCE during 4.42 ±0.583 years after PCI was 30.77% with 95%CI [27.01%; 34.73%].
- Significant portion of MACCE (15%) occurred during the first year of follow-up period after PCI. This period is also characterized by a higher level of Hazard rate compared to the subsequent years of observation.
- There were registered 93 cases (15.73%) of myocardial infarctions; 5 cases (0.87%) of stroke; 24 cases (4.2%) of cardiovascular death and 82 cases (14.34%) of repeated revascularization..

The objectives of this observational study were to estimate the rates of Major adverse cardiac and cerebrovascular events (MACCE), as well as to obtain data on patient's characteristics, drug therapy, lipid and inflammatory markers profile during long-term follow-up of patients underwent PCI with drug-eluting stents implantation. These objectives were met.

The present study was the follow-up of OPTIMA study aimed to investigate short-term outcomes after PCI in 602 patients received statins during coronary intervention. Follow-up data after a mean of 4.42 ± 0.583 years in OPTIMA II were obtained for 543 patients, analysis of MACCE was performed for 572 patients (95% from 602). During the long-term follow-up the incidence of MACCE after PCI was 30.77%, the cardiovascular death occurred in 4.2% of patients, myocardial infarction – in 15.73%, repeated revascularization was performed in 14.3% of patients.

According to data from other similar registries, the rate of MACCE in 1-5 years after PCI significantly varies (from 15 to 38%) and depends on study population (12, 13, 14, 15). Patients in the OPTIMA study present standard population of patients with stable coronary artery disease: male patients (80.6%) aged 60.22 years (at baseline) suffering from mild to moderate angina (more than two thirds had I-II functional class (FC) of angina at baseline), without signs of heart failure and very severe comorbidities. This stable course of CAD may account for relatively favorable prognosis and low death rate in the study population.

As expected, PCI in the study patients was associated with significant relief from angina: at the end of follow-up 4.42 ± 0.583 years after PCI. 61.6% of patients had no clinical signs of angina at all, 25.1% had angina pectoris I-II FC and only 13% had III-IV FC of angina. According to SAQ score, the majority of patients rated their angina frequency as minimal (median score - 100) and physical limitations due to angina - as minimal (median score – 88.83).

It is important that the significant portion of study patients during follow-up discontinued cardiovascular medications. In spite of the current guidelines on long-term medical therapy after myocardial revascularization, at the end of follow-up 4.42 ±0.583 years after PCI only 72.5% of patients received antiplatelet agents. Selective β-blockers were administered in 58.56% of patients, and approximately half of study participants (51%) received ACE inhibitors / ARA. These data are different from the

previous studies, including data of OPTIMA study investigators who reported that more than 80% of patients during 1 year after PCI continued to receive β-blockers and 87.2 – 92% - ASA (16, 17).

Regardless of positive effects of statins in improvement of prognosis and decrease of death and adverse cardiovascular events rate after PCI, treatment with statins was discontinued in nearly one fourth of patients participated in the OPTIMA study. At the time of enrolment in OPTIMA II study (mean time 4.42 ± 0.583 years after PCI) only 75.5% of patients received statins at baseline (during PCI) continued to be treated with at least one statin. It is noteworthy that the significant portion of patients discontinued statins as early as during first months after PCI. At the same time, LDL-C target level achievement (<1.8mmol/l) during follow-up was registered only in 7.7% of study patients; the median LDL-C level was 2.8 mmol/l.

Overall results:

- The observational study met its main objectives.
- Long-term follow-up of patients underwent PCI with drug-eluting stents implantation in clinical practice showed that MACCE rates were comparable to data of other similar trials and registries.
- Percutaneous coronary intervention in patients with stable CAD was associated with significant relief from angina and protection of heart systolic function. PCI resulted in increase of treatment satisfaction and improvement of quality of life in Russian patients.
- This “real-world” study reported relatively high incompliance of patients with optimal medical treatment during 4.42±0.583 years after PCI.
- The recommended lipid target level was not achieved in the vast majority of study patients.
- During long-term follow-up after PCI elevation of inflammatory markers was not registered in the study patients.