STUDY REPORT SYNOPSIS

ACS Registry

A non-interventional study to estimate the rates of outcomes in ACS patients in Moscow

Milestones:	Date of first subject in Q1 2018 (22 Mar 2018) Date of last subject in Q3 2020 (30 Sep 2020) Date of last subject last visit Q4 2021 (19 Oct 2021) Date of data base lock Q4 2021 (30 Nov 2021) Date of final report Q1 2022 (28 Mar 2022)
Phase of development:	Observational study
Sponsor:	AstraZeneca
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This study was performed in compliance with Good Clinical Practice (GCP) and Good Pharmacoepidemiology Practice (GPP).

The Investigator was perform the Observational Study in accordance with the regulations and guidelines governing medical practice and ethics in the country of the Observational Study and in accordance with currently acceptable techniques and know-how. The final protocol of the Observational Study, including the final version of the Subject Informed Consent Form, were approved and given a favourable opinion in writing by the Ethics Committee.

This submission/document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca (AZ) and opportunity to object.

Background/rationale

Cardiovascular diseases (CVD) are currently the leading cause of death in industrialized countries[11]. According to the official Russian statistics, in 2015, CVD was the cause in 34% of deaths in Russia[7]. Acute Coronary Syndrome (ACS) is the most prevalent manifestation of CVD and is associated with high mortality and morbidity. No other life-threatening disease is as prevalent or expensive to society[1]. In 2014 in Russian Federation 46 250 people died from acute myocardial infarction (MI) and 17 605 people died from recurrent MI[10].

ACS is a clinical syndrome characterized by unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). The most common cause of ACS is reduced myocardial perfusion that results from coronary artery narrowing caused by the formation of partially or totally occlusive thrombi in response to rupture of atherosclerotic plaques on the vessel wall[5,6,8].

In Russian Federation ACS management after ACS is provided in out-patient settings by doctors of different specialties (cardiologists and general practitioners (GPs)). However, the management of ACS in out-patient settings in some regions in Russian Federation is frequently suboptimal. Moscow city significantly differs from other parts of Russia from ACS management at hospital stage (up to 90% of PCI managed ST elevation myocardial infarction (MI) patients, no thrombolysis, short first medical contact to balloon time etc.) but it is unclear if management of post MI patients in Moscow out-patient settings is also optimal. In-hospital mortality in MI patients decreased last years but there is no data on clinical outcomes during 12 months after MI in Moscow.

This study provided the epidemiological data on cumulative incidence of major adverse cardiovascular and cerebrovascular events (MACCE) (MI, stroke, cardiovascular death) within 12 months after MI in real clinical practice in Moscow and described different patterns of DAPT in out-patient setting. The information received in this study will help to optimize management of Russian patients with ACS. The data will be used in discussion with payers.

Objectives

Primary objective:

The primary objective of this study is to describe the cumulative incidence of Major Adverse Cardiovascular and Cerebrovascular Events (MACCE) [MI, stroke, and cardiovascular death] observed over 1 year after index MI in all patients enrolled in the study.

Secondary objectives:

1. To describe the cumulative incidence of recurrent MI in all patients enrolled in the study over 1 year after index MI.

2. To describe the cumulative incidence of stroke in all patients enrolled in the study over 1 year after index MI.

3. To describe the cumulative incidence of cardiovascular death among all patients enrolled in the study over 1 year after index MI.

4. To describe the cumulative incidence of all-cause mortality among all patients enrolled in the study over 1 year after index MI.

5. To describe the cumulative incidence of recurrent MACCE (the second or consecutive event experienced by the same patient) among all patients enrolled in the study over 1 year after index MI.

6. To describe the cumulative incidence of repeated revascularization due to stent thrombosis among all patients enrolled in the study and managed invasively over 1 year after index MI.

7. To describe the cumulative incidence of MACCE following DAPT discontinuation/disruption/ interruption or switching to another P2Y12 inhibitor over the 1 year observational period among patients enrolled in the study who were taking DAPT.

8. To describe the proportion of patients on different DAPT (clopidogrel + ASA, ticagrelor + ASA, other combinations of ASA and P2Y12 inhibitors) over the 1 year observational period after index event among patients enrolled in the study who take DAPT.

9. To describe the DAPT duration in real clinical practice in Moscow city among patients enrolled in the study who take DAPT over 1 year after index MI.

10. To describe the cumulative incidence of DAPT discontinuation/ disruption/ interruption observed among patients on DAPT enrolled in the study and causes for the discontinuation/ disruption/ interruption over 1 year after index MI.

11. To describe the cumulative incidence of switching from one P2Y12 inhibitor to another among patients enrolled in the study over 1 year after index MI.

12. To describe causes of antiplatelet switching in real clinical practice among all patients enrolled in the study over 1 year after index MI.

13. To describe the proportion of patients achieving the target level of low-density lipoprotein (LDL) within 1 year of observation after the index event among patients enrolled in the study who are prescribed lipid lowering therapy.

14. To describe the proportion of post MI patients managed by various specialists (cardiologists, GPs, other specialized physicians) among all patients enrolled in the study.

Study design

This non-interventional multicenter observational study enrolled patients after myocardial infarction; the patients had been followed-up in outpatient settings in Moscow (47 cardiologists or GPs).

This observational project did not suggest any intervention into a routine clinical practice, including the choice of treatment modality or special methods of investigation. The study included only those patients who had signed the informed consent after explanation of the study objectives and methods by the study physician.

Medical data were obtained from medical records and patient reports starting from the patient's first visit to polyclinic after discharge from the hospital due to MI and thereafter at follow-up visits during 1-year period. Discharge letters or death certificates were the main data sources to obtain information on MACCE in this observational study.

Data source:

Patients enrolled in this study were visiting physicians in polyclinics for regular checkups and examinations in accordance to routine clinical practice. However, there were four scheduled follow up visits to the investigator of the study for examination and data collection. These follow up visits were scheduled as defined below: screening and enrollment visit was the first post MI patient's visit to polyclinic after discharge from the hospital. Subsequently, patients visited the polyclinic at 3, 6 and 12 months after index event.

In case of MACCE occurring within the observational period of 1 year, this information was obtained by the investigator from the discharge letter or death certificate. Information on any changes or discontinuation/disruption/interruption of DAPT and lipid profile data was also collected by the investigator from patients and their medical records. Investigator requested proactively patient's discharge letters and other related medical records in case if a patient reported recurrent MACCE or changes in the antithrombotic therapy and regimen of taking this therapy. Each patient enrolled in the study signed ICF and provided information to investigator on MACCE, DAPT changes. If requested by an investigator, patients provided required documents (reports from medical records, discharge letters) confirming reported events.

Study population

All consecutive patients who had survived myocardial infarction and who came for further treatment and observation to polyclinic after discharge from hospital were able to enroll in this study on condition that they provided a consent form. The total number of post MI patients enrolled in the study was 1586. All study subjects were observed in polyclinics of Moscow city within first year after index event.

Inclusion criteria

The subject population that was observed in this prospective study had to meet the following criteria:

1. Patients survivors who visited outpatient setting after discharge from hospital due to MI (STEMI or NSTEMI) within 1 month after discharge from hospital;

2. Obtained written informed consent for participation in this study.

3. Age of 18 year or older.

Exclusion criteria

1. Current participation in a clinical study.

2. Unknown type of MI

Statistical methods

Descriptive statistics included summary tables (n, mean, median, standard deviation, minimum and maximum, quartiles Q1 and Q3 for continuous variables and n, frequency and percentage for categorical values, and number of missing values for each variable presented).

No comparison was performed in the study, no correlation was estimated.

For the population estimation of the variables a two-sided 95% confidence interval (CI) was obtained.

Cumulative incidence of MACCE within 12 months from index MI was estimated by means of Kaplan-Meier analysis. Total number of MACCE events and number of events of each type (recurrent MI, stroke, cardiovascular death) including several MACCE in one patient were presented as proportions.

Primary and secondary variables related to MACCE and incidence of all-cause mortality were analysed in the overall study population and in subgroups of patients managed invasively/medically for index event.

Results: Enrolled Set was the principal analyzed population, comprising the subjects fully complying with selection criteria, who have provided signed Informed Consent Form for participation in the study.

Enrolled set included 1,586 subjects of which 1,321 have completed the study in compliance with the Protocol. Further analysis set did not include erroneously enrolled 10 subjects. Therefore, the enrolled set finally included 1,576 subjects.

Efficacy evaluation

Analysis of primary and secondary efficacy variables was carried out in the Enrolled Set and in the subgroups of subjects who underwent percutaneous coronary intervention (PCI) and conservative treatment in regards to index event, as well as in the subgroups of subjects included to the Registry before June 30th, 2019 and from July 01st, 2019. Additional analysis has been fulfilled for the subgroup of subjects who completed 12-months follow-up period without MACCE and hemorrhage occurrence that required hospitalization, medical intervention performance, discontinuation of DAPT or replacement of Ticagrelor / Prasugrel with Clopidogrel in respect to compliance with at least one of the following criteria or any combination of those:

- Age ≥ 65 years at the time of 12-months follow-up period termination;
- Presence of diabetes mellitus;
- Presence of chronic renal diseases;
- History of MI;
- Presence of multivessel disease of coronary arteries.

Mean age of enrolled subjects was 62.2 ± 11.1 years old with the minimum of 31 years old and maximum of 93 years old. The enrolled set included 1,088 men (69.0 %) and 488 (31.0 %) women. Mean body weight was 83.7 ± 15 kg and body mass index (BMI) was 28.6 ± 4.5 kg/m^2. Conservative treatment received 123 subjects (7.8 %); coronary artery bypass grafting underwent 20 subjects (1.3 %); and PCI underwent 1,433 subjects (90.9 %).

After index MI DAPT was prescribed to 1,537 subjects (97.5 %).

The primary efficacy endpoint

Cumulative incidence of MACCE for all subjects enrolled was 0.038 (95 % CI 0.027; 0.048), in subgroup of subjects who underwent PCI was significantly lower versus in subgroup of subjects treated conservatively (0.032 (95 % CI 0.022; 0.042) versus 0.110 (95 % CI 0.044; 0.176, correspondently), ***p***-value = 0.0002).

In regards to the subgroup of taking Clopidogrel, this value was 0.052 (95 % CI 0.034; 0.070). Patients taking Prasugrel demonstrated cumulative incidence equal to 0.031 (95 % CI 0.000;

0.074), Ticagrelor - equal to 0.025 (95 % CI 0.013; 0.037). A statistically significant difference was found between the Ticagrelor and Clopidogrel groups (p-value=0.032).

Secondary efficacy end points

Cumulative incidence of MACCE by type of event and reasons for DAPT discontinuation / disruption / interruption were calculated by means of competing risks method. Cumulative incidence of non-fatal MI among all subjects enrolled was 0.016 (95 % CI 0.009; 0.023); cumulative incidence of non-fatal stroke was 0.005 (95 % CI 0.001; 0.010); and cumulative incidence of cardiovascular deaths was 0.016 (95 % CI 0.010; 0.023).

As for the subjects who underwent the procedure of PCI, value of cumulative incidence of non-fatal MI was 0.014 (95 % CI 0.007; 0.020); cumulative incidence of non-fatal stroke was 0.006 (95 % CI 0.001; 0.011); and cumulative incidence of cardiovascular deaths was 0.013 (95 % CI 0.007; 0.019). With respect to the subjects treated conservatively, cumulative incidence of non-fatal MI was 0.047 (95 % CI 0.006; 0.087); and cumulative incidence of cardiovascular deaths was 0.064 (95 % CI 0.010; 0.117). Statistically significant differences were identified between subgroups of subjects who underwent PCI and were treated conservatively, with regards to cumulative incidence of non-fatal MI (*p*-value = 0.007) and cardiovascular deaths (*p*-value = 0.001).

Statistically significant differences were identified between subgroups of patients who took Clopidogrel, Prasugrel and Ticagrelor, with regards to cumulative incidence of cardiovascular deaths (0.027, 0.031 and 0.005, respectively, ***p***-value = 0.008). A statistically significant difference was found between the Ticagrelor and Clopidogrel groups (p-value=0.026) and between Ticagrelor and Prasugrel groups (p-value=0.037).

Total number of MACCE and number of major cardiovascular and cerebrovascular events by type

In regards to the Enrolled Set, 52 episodes of MACCE were registered throughout the study with 49 subjects (3.1 %): 22 non-fatal MI with 20 subjects (1.3 %); 7 non-fatal strokes with 7 subjects (0.4 %), and 23 (1.5 %) fatalities (subjects died by cardiovascular events).

Cumulative incidence of all-cause deaths, recurrent MACCE and recurrent revascularization observed within 1 year after index MI was estimated by means of Kaplan-Meier analysis.

There were 37 (2.3 %) all-cause deaths in total; 29 subjects (2.0 %) died among those who underwent PCI and 8 subjects (6.5 %) died in the subgroup of conservatively treated subjects. Cumulative incidence of all-cause deaths for all enrolled subjects was 0.026 (95 % CI 0.017; 0.034); for subjects underwent PCI - 0.021 (95 % CI 0.014; 0.029); and for concervatively treated subjects - 0.083 (95 % CI 0.023; 0.142).

Recurrent major cardiovascular and cerebrovascular events were reported with 3 subjects (0.2 %), all included to the subgroup of subjects who underwent the procedure of PCI. Cumulative incidence of this type of event was 0.002 (95% CI 0.000; 0.004). Cumulative incidence of recurrent revascularization observed within 1 year following index MI was 0.004 (95 % CI 0.001; 0.007).

Values of cumulative incidence of MACCE after DAPT discontinuation / disruption / interruption or switching to another P2Y12 inhibitor observed within 1 year of observation were observed with 18 subjects (1.2 %) (21 MACCE occurrences being 42 % of the absolute count of such events) initially receiving DAPT treatment who reported at least once DAPT discontinuation / disruption / interruption or switching to another P2Y12 inhibitor within 12-months follow-up period. Cumulative incidence constituted 0.074 (95 % CI 0.041; 0.107).

Number and proportion of patients receiving DAPT in 3, 6 and 12 months after index MI.

Prior to enrolment in the present study, 665 subjects (43.3 %) were treated with DAPT using Clopidogrel drug; 633 subjects (44.4 %) continued on this treatment schedule 12 months after MI. Prior to enrolment in this study, 792 subjects (51.5 %) were treated with DAPT based on Ticagrelor drug; 649 subjects (45.5 %) continued on this treatment schedule 12 months after MI. 82 subjects (5.3 %) before inclusion to the present study and 58 subjects (4.1 %) in 12 months adhered to an alternative DAPT treatment regimen.

Mean duration of DAPT treatment was 11.2 months.

Overall cumulative incidence of DAPT discontinuation / disruption / interruption in 12 months after MI was 0.104 (95 % CI 0.091; 0.118). The root cause of treatment interruption with highest cumulative incidence of 0.023 (95 % CI 0.018; 0.028) was the cost of medications. Statistically significant differences between subgroups of subjects included to the Registry before June 30th, 2019 and from July 01st, 2019 have been found with regards to the following reasons (p-value <0.05):

- Cost of medications in 3, 6 and 12 months after MI (p-value <0.001; <0.001; and <0.001, respectively);
- Patient's noncompliance with prescribed treatment in 3 and 6 months after MI (p-value 0.024 and 0.046, respectively).

Cumulative incidence of switching to another P2Y12 inhibitor in 12 months after MI was 0.004 (95 % CI 0.001; 0.005).

Target level of LDL. According to guidelines of European Society of Cardiology and European Atherosclerosis Society set forth in regards to dyslipidemia management [9], attainment of target level of LDL at Visit 3 (6 months after MI) and at Visit 4 (12 months after MI) was defined as lowering of LDL by more than 50 % from the baseline level (Visit 1). Actual concentration level at the visit should not have exceeded 1.4 mmol/L. 54 subjects (3.5 %) attained target level of LDL in 6 months following index MI, and 51 subjects (3.3 %) reached the target level in 12 months after MI.

Specialization of treating physician. All subjects (1,576) after index event occurrence were managed in the outpatient settings by the physicians specialized in the cardiology field

Additional analysis of subgroup of subjects who completed 12-months follow-up period without complications.

In the present case, complications mean development of any MACCE and/or hemorrhage occurrence that required hospitalization, medical intervention performance, discontinuation of DAPT or replacement of Ticagrelor / Prasugrel with Clopidogrel.

Out of 1,576 subjects enrolled in the study 1,514 subjects (96.0 %) have completed 12-months observation period without complications. Additional analysis implied investigation of presence in subjects' history of such factors as higher risk of ischemic events, elderly age ≥ 65 years, diabetes mellitus, chronic renal diseases, medical history of MI (except for index MI), and multivessel disease of coronary arteries. 248 subjects (16.4 %) did not have any factors in their histories, while 7 subjects (0.5 %) had all of them. 646 subjects (42.7 %) were of the elderly age; 319 subjects (21.1 %) had the diagnosis of diabetes mellitus. Chronic renal diseases were diagnosed with 282 subjects (18.6 %); 241 subjects (15.9 %) had MI in the history; and 920 subjects (60.8 %) suffered from multivessel disease of coronary arteries.

Safety evaluation

In total, there were 243 AEs reported with 183 subjects (11.6 %). In 82 cases the observed AEs were mild; in 70 cases AEs were moderate; and in 91 - severe. In 36 cases AEs resulted in discontinuation / disruption / interruption of DAPT. As well, there were 145 SAEs. In 30 cases AEs were the cause of death of the subject.

33 AEs reported with 29 subjects (1.8 %) had at least possible causal relationship with DAPT. In 26 cases AEs were mild; in 4 cases AEs were moderate; and in 3 - severe. In 26 cases adverse events required discontinuation / disruption / interruption of dual antiplatelet therapy. As well, there were 4 cases of SAEs probably related to DAPT. There were no AEs related to DAPT with lethal outcome.

The most frequently AEs (in 5 or more subjects) were registered in the SOCs Cardiac Disorders, Respiratory, Thoracis and Mediastinal Disprders and Infections and Infestations.

Below is presented the list of AEs possibly related to DAPT, in the opinion of the Investigators:

- Epistaxis: 7 subjects (0.4 %);
- Dyspnea: 6 subjects (0.4 %);
- Subcutaneous hematoma: 3 subjects (0.2 %);
- Hemorrhoid bleeding, gastrointestinal bleeding, and hematoma: 2 subjects (0.1 %);
- Pain in upper abdominal areas, hemorrhoids, gastric ulcer hemorrhage, presence of blood in the urea, hemoptysis, pulmonary hemorrhage, exertion dyspnea, post-hemorrhagic anemia, intraocular hemorrhage, hematuria, uterine hemorrhage: 1 subject (0.1 %).

Altogether, there were 145 SAEs reported with 115 subjects (7.3 %).

The most frequently registered SAEs were:

- Cardiac disorders: 74 SAEs in 66 subjects (4.2 %);
- Infections and infestations: 13 SAEs in 13 subjects (0.8 %);
- Benign, malignant and unspecified neoplasms (including cysts, polyps): 16 SAEs in 13 subjects (0.8 %).

There were 4 subjects (0.3 %) with SAEs related to DAPT of which 2 subjects (0.1 %) had gastrointestinal disorders; and 2 subjects (0.1 %) had respiratory, thoracic and mediastinal disorders.

Conclusion: The following rates of outcomes were registered during 1 year in the observational study in subjects survived from MI in Moscow:

Cumulative incidence of MACCE was 0.038 (95 % CI 0.027; 0.048).

Overall number of MACCE was 12 in 12 (0.8%) subjects in 3 months, 13 in 13 (0.8%) subjects in 3 - 6 months, 27 in 26 (1.6%) subjects after 6 months and 52 in 49 (3.1%) subjects during 12 months.

Number of non fatal MI was 6 in 6 (0.4%) subjects in 3 months, 3 in 3 (0.2%) subjects in 3 - 6 months, 13 in 12 (0.8%) subjects after 6 months and 22 in 20 (1.3%) subjects during 12 months.

Number of non fatal stroke was 1 in 1 (0.1%) subjects in 3 months, 2 in 2 (0.1%) subjects in 3 - 6 months, 4 in 4 (0.3%) subjects after 6 months and 7 in 7 (0.4%) subjects during 12 months.

Number of cardiovascular deaths was 5 in 5 (0.3%) subjects in 3 months, 8 in 8 (0.5%) subjects in 3 - 6 months, 10 in 10 (0.6%) subjects after 6 months and 23 in 23 (1.5%) subjects during 12 months.

Cumulative incidence of non fatal MI was 0.016 (95 % CI 0.009; 0.023).

Cumulative incidence of non fatal stroke was 0.005 (95 % CI 0.001; 0.010).

Cumulative incidence of cardiovascular death was 0.016 (95 % CI 0.010; 0.023).

Cumulative incidence of all-cause mortality was 0.026 (95 % CI 0.017; 0.034).

Cumulative incidence of recurrent MACCE (the second or consecutive event experienced by the same subject) was 0.002 (95 % CI 0.000; 0.004).

Cumulative incidence of repeated revascularization due to stent thrombosis was 0.004 (95 % CI 0.001; 0.007).

Cumulative incidence of MACCE following DAPT discontinuation/ disruption/ interruption or switching to another P2Y12 inhibitor was 0.074 (95 % CI 0.041; 0.107).

Number and proportion of subjects on Clopidogrel + Acetylsalicylic Acid was 707 (46.9%) 3 months after MI, 694 (47.3%) 6 months after MI, 633 (44.4%) 12 months after MI. Number and proportion of subjects on Ticagrelor + Acetylsalicylic Acid was 733 (48.6%) 3 months after MI, 692 (47.2%) 6 months after MI, 649 (45.5%) 12 months after MI. Number and proportion of subjects on Prasugrel + Acetylsalicylic Acid was 68 (4.5%) 3 months after MI, 62 (4.2%) 6 months after MI, 58 (4.1%) 12 months after MI.

Mean DAPT duration in the real clinical practice in Moscow among subjects on DAPT was 11.2 months.

Cumulative incidence of DAPT discontinuation/ disruption/ interruption due to bleeding events at 3 months was 0.002 (95% CI 0.000; 0.003), at 6 months was 0.004 (95% CI 0.002; 0.006), at 12 months was 0.006 (95% CI 0.003; 0.009).

Cumulative incidence of DAPT discontinuation/ disruption/ interruption due to various causes other than bleeding at 3, 6, 12 months after index MI was:

due to *Selective Surgery or Emergency Surgical Interventions* 0.0006 (95% CI 0.000; 0.001), 0.0006 (95% CI 0.000; 0.001) and 0.0010 (95% CI 0.000; 0.002);

due to *Other Adverse Events* 0.002 (95% CI 0.000; 0.003), 0.002 (95% CI 0.000; 0.004) and 0.004 (95% CI 0.002; 0.006);

due to *Subject's decision* 0.008 (95% CI 0.005; 0.011), 0.014 (95% CI 0.010; 0.018) and 0.018 (95% CI 0.013; 0.023);

due to *Cost of Medicaion* 0.012 (95% CI 0.009; 0.016), 0.020 (95% CI 0.015; 0.025) and 0.023 (95% CI 0.018; 0.028);

due to *Conditions Necessitating Administration of Oral Anticoagulants* 0.006 (95% CI 0.003; 0.008), 0.008 (95% CI 0.005; 0.011) and 0.010 (95% CI 0.007; 0.014);

due to *Patient's Noncompliance with Prescribed Treatment* 0.005 (95% CI 0.003; 0.008), 0.006 (95% CI 0.003; 0.008) and 0.006 (95% CI 0.004; 0.009);

due to *Other Reasons* 0.014 (95% CI 0.010; 0.018), 0.019 (95% CI 0.014; 0.023) and 0.021 (95% CI 0.016; 0.027).

Cumulative incidence of switching to another P2Y12 inhibitor at 3, 6, 12 months was 0.003 (95% CI 0.001; 0.005), 0.003 (95% CI 0.001; 0.005) and 0.004 (95% CI 0.001; 0.005).

Number and proportion of subjects reaching the target level of LDL among subjects who were prescribed lipid lowering therapy was 51 subjects (3.3 %).

Number and proportion of subjects who were managed by a cardiologist, GP, and other physicians in out-patient setting was all 1,576 subjects (100%).

Publications: None.