Non-Interventional Study (NIS) Report Synopsis

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EPICOR-RUS. Long-tErm follow-uP of antithrombotic management patterns In Acute CORonary Syndrome patients in RUSsia

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AstraZeneca

NIS REPORT SYNOPSIS

EPICOR-RUS. Long-tErm follow-uP of antithrombotic management patterns In Acute CORonary Syndrome patients in RUSsia

Sites and number of patients

Number of sites and subjects planned

600 patients were planned to be included in the study at 35 participating institutions (a minimum of 10 patients from each institution was expected). One site was closed prematurely based on the Sponsor's decision due to low enrollment rate, therefore 34 institutions participated. The sample size was based on anticipating of 5 comparisons to strategies that would be used by at least 10% of the population, in order to ensure a 80% power with a two-sided type I error of 1% (corresponding to a Bonferroni correction for 5 comparisons) to detect a relative risk of at least 1.5 for the comparison of two of these groups, assuming a 2-year event rate of 10% for the primary event. This sample size calculation is required to estimate probabilities of 50% with a two sided confidence interval that will extend in +/- 4% and +/- 3% from the observed proportion, respectively.

Number of subjects included in the analysis

The study enrolled 600 patients but one patient (# 1510) was removed from the final analysis based on the Sponsor's decision, due to non-compliance to study inclusion/exclusion criteria. Therefore, 599 patients were included in the final analysis in 34 participating institutions.

Study purpose

The purpose of the study was a description of the short- and long-term Antithrombotic Management Patterns (AMPs) in a real-life setting for patients hospitalised with an acute coronary syndrome (ACS) with documentation of clinical outcomes and their impact on the quality of life in a 'real-life' setting.

Study design

Multi-centre, observational, prospective, longitudinal cohort study included adult patients, in a real-life setting, hospitalised for ACS within 24 hours of symptom onset and with a final diagnosis of STEMI (ST-segment elevation myocardial infarction), NSTEMI (Non-ST-segment elevation myocardial infarction) or UA (unstable angina).

Each patient was followed for 24 months. Data collection was split up into acute phase and long-term follow-up after discharge from the hospital. At the acute phase eligible patients were sequentially invited to participate when he/she was going to be discharged (inter-hospital transfers were not considered as discharges) and consenting patients were requested to read and sign the Informed Consent Form. Demographic data, medical history, previous medications and health care consumption, management patterns including emergency reperfusion, coronary procedures and interventions, antithrombotic treatment patterns and the occurrence of any complications during the initial hospitalisation were collected. Long term

follow-up was performed up to 24 months after the index event: the patients were contacted by telephone at six weeks and every 6 months. Thrombo-embolic and/or bleeding events, hospitalisations or interventions, cardiovascular events, deaths were collected. Quality of Life (EQ-5D questionnaire) was evaluated before discharge and during follow-up phase.

Study participants

Subject sample was extracted from the typical cardiologic population hospitalised and diagnosed with ACS in a routine practice, provided written Informed Consent for participation in this study and able for follow-up contacts.

Inclusion criteria

1. Written informed consent has been provided.
2. Contact Order Form has been provided
3. Aged 18 years or older.
4. Diagnosis of STEMI, NSTEMI or UA confirmed using the following definitions:

   Criteria for STEMI diagnosis

   a) History of chest pain/discomfort and
   b) Persistent ST-segment elevation (> 30 min) of ≥ 0.1 mV in 2 or more contiguous ECG leads or presumed new LBBB (Left bundle branch block) on admission and
   c) Elevation of cardiac biomarkers (CK-MB, troponins): at least one value above the 99th percentile of the upper reference limit.

   Criteria for NSTEMI diagnosis:

   a) History of chest pain/discomfort and
   b) Lack of persistent ST-segment elevation, LBBB or intraventricular conduction disturbances and
   c) Elevation of cardiac biomarkers (CK-MB, troponins): at least one value above the 99th percentile of the upper reference limit.

   Criteria for Unstable Angina diagnosis :

   a) Symptoms of angina at rest or on minimal exercise and
   b) (Transient) ST-T changes and
   c) No significant increase in biomarkers of necrosis but objective evidence of ischaemia by non-invasive imaging or significant coronary stenosis (at angiography).
5. Hospitalised within 24 hours of onset of symptoms or transferred from another hospital within 24 hours of the onset of symptoms.

Exclusion criteria*:*

1. UA, STEMI and NSTEMI precipitated by or as a complication of surgery, trauma, or gastrointestinal (GI) bleeding or post-PCI (percutaneous coronary intervention).
2. UA, STEMI and NSTEMI occurring in patients already hospitalised for other reasons.
3. Presence of any condition/circumstance which in the opinion of the investigator could significantly limit the complete follow up of the patient (e.g. tourist, non-native speaker or does not understand the local language, psychiatric disturbances).
4. Already included in the EPICOR-RUS study.
5. Presence of serious/severe co-morbidities in the opinion of the investigator which may limit short term (i.e. 6 month) life expectancy.
6. Current participation in a clinical trial.

Evaluation variables

Primary study variable:

Short- and long-term Antithrombotic Management Patterns (AMPs) in a real-life setting for patients hospitalised with an acute coronary syndrome (STEMI, NSTEMI, UA).

Secondary study variables:

- Impact of AMPs on clinical outcomes and quality of life in a 'real-life' setting;
- Variations in the acute clinical management and AMPs and relation between AMPs and in-hospital outcomes;
- Variations in AMPs for STEMI and NSTE-ACS patients between the hospital discharge index event 1 year and 2 years later and comparison clinical outcomes over a 2-year period;
- Determinants of AMP choices in the acute phase of the index event and up to two years thereafter;
- Incidence of bleeding complications associated with the different AMPs;
- Discontinuation (including temporary one) rate for antithrombotic medications prescribed at discharge;
- Reasons for transferring patients to a PCI centre and comparing short- and long-term outcomes;
- Impact of the different AMPs on quality of life.

Statistical analysis methods

General methods

Baseline data (demographic, clinical characteristics etc.) are presented for the whole study sample. Study results are provided separately for 3 diagnosis groups (STEMI, NSTEMI or UA) in a descriptive way (n, mean, median, standard deviation, minimum and maximum for continuous variables and n, frequency and percentage for categorical values). Missing data were not replaced.

Primary variable

Different AMPs were evaluated separately for each treatment phase for each diagnosis group. Number and percentage of patients who continued each AMP type were calculated for each follow-up contact.

Secondary variables

Patients were divided into subgroups within each diagnosis (taking antiplatelet monotherapy/ double therapy (2 antiplatelets), underwent PCI/conservative treatment, underwent thrombolytics/not for STEMI group only). Clinical outcomes rate during follow-up was calculated for number of valid cases for each follow-up contact from discharge to 24 months and these endpoints were cumulative (i.e. cases of death at 6 months were calculated as those in the period from 0 to 6 week + in the period from 6 week to 6 month).

Rate of outcomes, QoL were compared between subgroups of different AMP, different hospital type. Frequency variables were compared between different subgroups using Chi-square criterion. P-value was reported for the comparison at two-sided level of significance of 0.05.

RESULTS

Target analysis population

Of 600 enrolled patients 558 completed the study according to protocol, 42 early terminated participation in the study; 1 patient was excluded from the analysis. Statistical analysis was performed on a single intent-to-treat population (n=599). Predefined diagnosis groups included patients with STEMI (n=375), NSTEMI (n=147) and UA (n=77). 232 patients were admitted to general hospitals, 160 – to regional hospitals, 156 patients – to university hospitals and 51 patients – to other types of hospitals.

Demographics and clinical characteristics

Studied population consisted of 426 (71.1%) men and 173 (28.9%) women. The mean (± SD) age of the patients was 60.1 ± 11.9 years; the mean height was 170.8 ± 8.6 cm and the mean weight was 81.4 ± 14.2 kg.

Risk factors of cardiovascular diseases included: arterial hypertension 81.3% (477/587); hypercholesterolemia 54.1% (283/523); diabetes mellitus 14.3% (85/595), family history of coronary artery disease 29.7% (148/499). 227 (37.9%) patients were current smokers; 82 (13.7%) were ex-smokers, 44.9% (269) have never smoked and for 21 (3.5%) patients the smoking status was unknown.

57.8% (344/595) patients had cardiovascular disease(s) (CVD) before participation in the study (most common ones were chronic angina 41.9% (249/594), previous myocardial infarction (MI) 23.1% (138/597). 43.8% (260/594) patients had other concomitant (non-cardiovascular) diseases (most common were COPD 14.5% (87/598) and peptic ulcer 13.0% (78/698)).

Within previous 3 months before the inclusion to the study 26.8% (158/590) patients were taking antiplatelet(s) (Aspirin (157; 26.6%), Clopidogrel (36; 6.1%) and Ticlopidine (1; 0.2%)); 1.0% (6/591) patients were taking anticoagulant(s) (Warfarin (5; 0.8%), Enoxaparin (1 patient), and Heparin (1 patient)). Most common other cardiologic drugs were: beta-blockers (147; 25.0%), angiotensin-converting-enzyme inhibitors/ angiotensin receptor blockers (195; 33.2%), statins (67; 11.4%), Ca^{2+}-channel blockers (54; 9.2%), non-loop diuretics (4; 8.0%).

In pre-hospital setting, as anticoagulants, 54.1% (317/586) patients received unfractionated heparin; 5.3% (31/587) – low-molecular-weight (LMW) Heparin and 0.2% (1/589) - Fondaparinux.

Primary objective

<u>Antithrombotic Management Patterns (AMPs) for each diagnosis groups</u>

In a real-life setting for patients hospitalised with ACS AMPs were presented mostly as a combination of Aspirin and Clopidogrel (double therapy) during hospitalisation and at discharge, but in pre-hospital setting most of the patients received antiplatelets monotherapy.

In STEMI group (n=375) double-therapy was administered in 126 (33.6%) patients in pre-hospital setting, 320 (85.3%) during hospitalisation and 337 (89.9%) at discharge. Aspirin monotherapy was administered in 160 (42.7%), 29 (7.7%) and 28 (7.5%) patients, and Clopidogrel monotherapy in 17 (4.5%), 3 (0.8%) and 6 (1.6%) patients, correspondingly. Antagonists of the platelet glycoprotein (GP) IIb/IIIa receptor (GPIIb/IIIa) were administered during hospitalisation in 20 (5.3%) patients.

In NSTEMI group (n=147) double-therapy was administered in 19 (12.9%) patients in pre-hospital setting, 109 (74.1%) during hospitalisation and 115 (78.2%) at discharge. Aspirin monotherapy was administered in 68 (46.3%), 32 (21.8%) and 30 (20.4%) patients, and Clopidogrel monotherapy in 4 (2.7%), 3 (2.0%) and 2 (1.4%) patients, correspondingly. Antagonists of GPIIb/IIIa were administered during hospitalisation in 3 (2.0%) patients.

In UA group (n=77) double-therapy was administered in 16 (20.8%) patients in pre-hospital setting, 64 (83.1%), during hospitalisation and 64 (83.1%) at discharge. Aspirin monotherapy was administered in 30 (39.0%), 11 (14.3%) and 12 (15.6%) patients. Clopidogrel monotherapy was administered in 1 (1.3%) patient during hospitalisation and antagonists of GPIIb/IIIa were administered during hospitalisation in 1 (1.3%) patient only.

Number and percentage of usage of antiplatelets loading doses in percutaneous intervention (PCI) and non-interventional groups during in-hospital phase

During in-hospital phase in the PCI group (n=339) and non-PCI group (n=259) Clopidogrel in loading doses was prescribed to 237 (69.9%) and 80 (30.9%) patients; Aspirin in loading doses - 76 (22.4%) and 72 (27.8%) patients. GPIIb/IIIa antagonists were administered in PCI group only, in 24 (7.1%) patients: 14 (4.1%) received Eptifibatide in loading doses, 10 (2.9%) patients received F(ab')2 fragment of anti-GPIIb/IIIa monoclonal antibody. One patient in non-PCI group received Dipyridamole.

Number and percentage of AMPs for each diagnosis groups

241 (64.3%) patients with STEMI, 54 (36.7%) with NSTEMI and 44 (57.1%) with UA underwent PCI. In STEMI group only, 146 (38.9%) patients received thrombolytics (at the pre-hospital setting or in-hospital phase): 40 (10.7%) received Streptokinase, 45 (12.0%) - t-PA (tissue plasminogen activator); 1 (0.3%) - r-PA (recombinant plasminogen activator); 39 (10.4%) - TNK-tPA (tenecteplase t-PA); 21 (5.6%) - other thrombolytics.

Number and percentage of patients with cancellation of antiplatelets during 2 years after discharge

Aspirin monotherapy prescribed at discharge was cancelled in 1.4% (1/70) patients, Clopidogrel monotherapy prescribed at discharge – in 12.5% (1/8) patients. In the subgroup of patients who were prescribed double therapy at discharge Aspirin was cancelled in 10.3% (53/516) and Clopidogrel was cancelled in 53.5% (276/516) patients. Among patients who were prescribed both antiplatelet and anticoagulant at discharge the treatment was cancelled in 53.8% (7/13) patients.

Secondary objectives

1. The impact of AMPs on clinical outcomes and quality of life

In STEMI group: the subgroup of patients who received antiplatelets double therapy during hospitalisation compared to the rest of patients was characterised by lower rate of heart failure (60.0% vs 33.1%, $p < 0.001$); similar data were obtained in patients who received double therapy at discharge (50,0% vs 35,6%, $p = 0.082$). In NSTEMI group the patients who received double therapy during hospitalisation as well as the subgroup who received double therapy at discharge had lower rate of heart failure (32.1% vs 65.8%, $p < 0.001$ and 33.9% vs 65.6%, $p < 0.001$) compared to the rest of patients, but higher rate of hospitalization/physician office visit due cardiovascular event at 24 months (65.4% vs 40.0%, $p = 0,008$ and 66.1% vs 33.3%, $p < 0.001$). The subgroup underwent PCI had lower rate of

heart failure (24.1% vs 50.5%, p = 0.002) and the subgroup without thrombolytics and PCI had higher rate of heart failure (50.0% vs 25.5%, p = 0.003).

In UA group the subgroup of patients who received double therapy during hospitalisation was characterised by lower rate of atrial fibrillation/flatter (0.0% vs 15.4%, p < 0.001) compared to the rest of patients with UA.

2. Variations in the acute clinical managements and AMPs and relation between AMPs and in-hospital outcomes

Subgroups of patients who were admitted to regional hospital and university hospital were characterised by the highest proportion of patients who were underwent PCI (73.8% in STEMI group and 71.7% in NSTEMI/UA group for regional; 76.6% and 41.9% for university; 51.9% and 31.3% for general; 51.2% and 30.0% for other types of hospital). Double antiplatelets therapy during hospitalisation was assigned similarly often (more than 70% of patients) across all types of hospitals. The highest rate of thrombolytics usage was observed at other types of hospitals (73.2%) when at general, regional and university hospitals such proportion was 34.6%, 32.7% and 37.2% (STEMI group was assessed only).

In-hospital cardiac outcomes: in the subgroup who underwent PCI MI/Recurrent MI was more frequently than in the subgroup of conservative treatment (10.0% vs 3.8%, p = 0.004) but heart failure rate was lower (30.1% vs 39.6% p = 0.015). In the subgroup received double therapy with antiplatelets heart failure rate was lower than in the subgroup received one antiplatelet (29.4% vs 55.0%, p < 0.001); in the STEMI group the rate of MI/recurrent MI was higher than in NSTEMI/UA group (9.1% vs 3.2%, p = 0.007).

3. Variations in AMPs for STEMI and NSTE-ACS patients between the hospital discharge index event 1 year and 2 years later and comparison clinical outcomes over a 2-year period

There were differences (p < 0.001) between STEMI and NSTEMI groups in the proportion of patients prescribed at discharge with monotherapy and double therapy (9.2% and 90.8% in STEMI; 21.8% and 78.2% in NSTEMI group), but such proportion was not different between the groups STEMI and UA (where 15.8% received monotherapy and 84.2% double therapy) or between NSTEMI and UA.

In subgroups of patients who were prescribed monotherapy or double therapy at discharge 98.7% and 98.6% patients correspondingly were alive at 12 months after index event and 97.2% and 99.0% patients were alive to 24 months. CV related death occurred in 1.3% (1) and 0.8% (4) patients at 12 months and 2.8% (2) and 0.8% (4) patients at 24 months. Cardiac surgery reported in 2.7% and 4.3% patients at 12 months and 2.8% and 5.7% patients at 24 months; hospitalization/physician office visit due cardiovascular event in 40.0% and 52.7% at 12 months and 45.1% and 57.2% at 24 months; hospitalization/physician office visit due bleeding event in 0.0% and 1.6% at 12 months and 0.0% and 2.0% at 24 months.

4. Determinants of AMP choices in the acute phase of the index event and up to two years thereafter

The subgroup of patients who underwent PCI (n=339) was characterised by high frequency of double therapy administration (88.2% and 4.5% in conventional treatment subgroup), high

frequency of Clopidigrel administration (95.9% and 76.8% correspondingly). GPIIb/IIIa antagonists were administered in PCI subgroup only. The most often prescribed anticoagulant was Unfractionated heparin (at loading dose in 32.2%; at maintenance dose in 60.5% patients in PCI subgroup and in 35.1% and 72,4% patients in non-PCI subgroup respectively); LMW Heparin, Fondaparinux, Bivalirudin, Warfarine were administered less frequently and Acenocumarol was not prescribed.

Frequency of different PCI types: Primary/direct intervention (immediate mode of reperfusion in acute MI (AMI)) was the most common PCI type (46.6% in the subgroup who were underwent PCI). Rescue PCI (after failed thrombolysis where failed refers to ischemic discomfort and/or lack of ST elevation) was done in 12.7% patients; facilitated PCI (immediate following successful thrombolysis or in conjunction with thrombolysis) in 5,0% patients. 11.8% patients received PCI for treatment of unstable angina, 5.3% for post AMI ischemia and 0.6% for cardiogenic shock (early PCI). In the subgroup of patients who underwent thrombolysis 50.6% received rescue PCI, 20.0% facilitated PCI; 5.9% non-emergent adjunctive PCI of non-culprit lesion (stayed) and 21.2% patients received other PCI types (including non-emergent elective PCI of suspected culprit lesion).

5. Incidence of bleeding complications associated with the different AMPs

In subgroups of patients (underwent thrombolysis, received double therapy, GPIIb/IIIa antagonists, anticoagulants, any antiplatelet and any anticoagulant during hospitalisation) vascular access and/or other types of bleeding were the most common among four types (gastrointestinal, genitourinary, vascular access, other).

6. Discontinuation (including temporary one) rate for antithrombotic medications prescribed at discharge

The rate of discontinuation of antiplatelets was not high. To 12 months of follow-up Aspirin was cancelled in 1.5% patients and Clopidogrel in 14.5% patients; to 24 months Aspirin was cancelled in 1.0% patients and Clopidogrel in 5.7% patients. The most common reasons for treatment cancellation were surgical intervention, hospitalisation and recommendation of a doctor.

7. Reasons for transferring patients to a PCI centre and comparing short- and long-term outcomes

572 (95.5%) patients were not transferred to other hospitals. Among 27 patients who were transferred to a second hospital the rate of short-term cardiac outcomes did not differ between patients with cardiac cath or CABG at in-hospital phase (n = 22) and without cardiac this reason for transfer. 2 patients with cerebrovascular event were reported in the subgroup with cardiac cath or CABG at in-hospital phase.

8. Impact of the different AMPs on quality of life

The subgroup of patients who were prescribed double antiplatelets therapy had significantly ($p < 0.05$) higher proportion of patients without disturbances of QoL assessed by EQ-5D scales at discharge from the hospital and during follow-up contacts up to 24 months from the event.