NIS REPORT SYNOPSIS

EPICOR: Long-term follow-up of antithrombotic management patterns in acute coronary syndrome patients

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: NOT APPLICABLE

ACTIVE INGREDIENT: NOT APPLICABLE

Study No: NIS-CEU-DUM-2009/1 **NCT:** Not Applicable
TITLE: Long-term follow-up of antithrombotic management patterns in acute coronary syndrome patients

Developmental Phase: NOT APPLICABLE

Study Completion Date: Last Patient Last Visit (last visit date for data included in this report): 31 March 2013

Date of Report: 20 March 2014

OBJECTIVES:

The primary objectives were:

- To describe the short- and long-term antithrombotic management patterns (AMPs) in a real-life setting for patients hospitalized with an acute coronary syndrome (i.e., ST-segment elevation myocardial infarction [STEMI], unstable angina/non-ST-segment elevation myocardial infarction [UA/NSTEMI]).

Secondary objectives of the study were:

- To compare the impact of AMPs on clinical outcomes, economic costs, and quality of life (QoL) in a real-life setting.

- To describe the variations in the acute clinical management and AMPs of patients hospitalized for STEMI or UA/NSTEMI and to compare the in-hospital clinical outcomes (i.e., ischemic and bleeding events) between sites and countries.

- To describe the variations in AMPs for STEMI and UA/NSTEMI patients between the hospital discharge following the index event and 2 years later and to compare clinical outcomes (ischemic and bleeding) over a 2-year period between sites and countries.

- To estimate the STEMI and UA/NSTEMI associated health care resource consumption and related costs during the hospitalization for the index event, and up to 2 years after hospital discharge. In addition, to describe its components (short- and long-term costs of the specific disease management including hospital stay, medical transportation, medical

treatments and procedures, visits to any health care provider and costs related to the disease outcomes and treatment-associated events).

- To evaluate the determinants of AMP choices in the acute phase of the index event and up to 2 years thereafter (i.e., patient's characteristics, hospital characteristics, coronary intervention strategies and type of coronary stents used, local payment/reimbursement systems, type of healthcare system, and economic environment).

- To describe the incidence of bleeding complications (by type/severity/timing) associated with the different AMPs, and to estimate the AMP-associated bleeding risks.

- To evaluate the impact of specific clinical and non-clinical events during the 2-year follow-up (e.g., bleeds, planned and non-planned medical interventions) on antithrombotic treatment interruptions, and on the occurrence of subsequent thrombo-embolic events.

- To describe reasons for transferring patients to a percutaneous coronary intervention (PCI) centre (i.e., primary PCI for STEMI patients or early PCI in UA/NSTEMI patients) and to compare their short- and long-term clinical outcomes with those of patients who receive a conservative in-hospital management for the index event.

- To evaluate the impact of the different AMPs on QoL.

- To document compliance with the international guidelines for AMP use.

METHODS:

EPICOR was a multinational, multicentre, observational, prospective, longitudinal cohort study which included patients, in a real-life setting, who were hospitalized for acute coronary syndrome (ACS) within 24 hours of symptom onset and who had a final diagnosis of UA, STEMI, or NSTEMI and survived to discharge. Participating countries included Argentina, Belgium, Brazil, Denmark, Finland, France, Germany, Greece, Italy, Luxembourg, Mexico, Netherlands, Norway, Poland, Romania, Slovenia, Spain, Turkey, UK, and Venezuela.

In order to obtain a real-life overview of the medical management of ACS patients in each country, different treatment patterns within each country were reflected in the selected sites and within the proportion as they were provided to ACS patients in a real-life setting.

The study design was split into 2 phases:

- Acute phase during which pre-hospital and in-hospital data collection occurred (through hospital discharge for the index ACS event that triggered recruitment), and

- Follow-up phase (up to 2 years post discharge), during which information was obtained through telephone interviews.

Data were collected using an electronic CRF. Monitoring activities in a random sample of sites (at least 10% in each country) were conducted to ensure quality control, including checks of signed informed consent forms and source data verification.

A descriptive analysis approach (including frequency tables) was used, obtaining a 2-sided 95% confidence interval (CI) for the population estimation of the variables. All calculations and summaries were produced using SAS Version 9.2 (SAS 2009). All statistical tests performed were 2-tailed with significance determined by reference to the 5% significance level, unless otherwise stated. Differences between groups were assessed using appropriate statistical tests; standard n-sample comparisons between the groups were carried out using the following methods, unless otherwise specified: categorical data were compared using a Pearson's chi-squared test, except in the case where there was a single response level of

interest and the absolute number of events in each group was less than 10, in which case Fisher's exact test was used instead. Continuous data were compared by fitting an *n*-sample analysis of variance model; a non-parametric alternative may have been used where the data were not normally distributed. Normality assumptions were tested using the Shapiro-Wilk test of normality.

RESULTS:

Pre-Hospital and In-Hospital Data (Acute Phase)

Baseline characteristics: A total of 10,568 patients were included in the overall analysis. Demographic characteristics were as follows:

		STEMI (N = 4,943)	UA/NSTEMI (N = 5,625)	Total (N = 10,568)
Sex	Male	3,924 (79.4%)	3,996 (71.0%)	7,920 (74.9%)
Race	Caucasian	4,026 (81.4%)	4,784 (85.0%)	8,810 (83.4%)
Age	Mean (SD)	59.4 (12.09)	63.8 (12.06)	61.8 (12.27)

NSTEMI=non-ST-segment elevation myocardial infarction; SD=standard deviation; STEMI=ST-segment elevation myocardial infarction; UA=unstable angina

Site characteristics: Patients were enrolled in a total of 555 hospitals, with the following characteristics:

	STEMI (N = 4,943)	UA/NSTEMI (N = 5,625)	Total (N = 10,568)
Center Type			
Regional/Community/Rural	964 (19.5%)	1,298 (23.1%)	2,262 (21.4%)
Non-University General Hospital	1,427 (28.9%)	1,585 (28.2%)	3,012 (28.5%)
University General Hospital	1,965 (39.8%)	2,181 (38.8%)	4,146 (39.2%)
Other	587 (11.9%)	561 (10.0%)	1,148 (10.9%)
Hospital Facilities			
Cath Lab Facility	4,027 (81.5%)	4,280 (76.1%)	8,307 (78.6%)

Cath=catheterization; NSTEMI=non-ST-segment elevation myocardial infarction; STEMI=ST-segment elevation myocardial infarction; UA=unstable angina

Medical history: Cardiovascular (CV) risk factors were present in the majority of patients, with hypertension, hypercholesterolemia, and smoking being the most prevalent. Overall, 35% of the patients had previous cardiovascular disease (CVD), as shown in the following table:

	STEMI (N = 4,943)	**UA/NSTEMI (N = 5,625)**	**Total (N = 10,568)**
Presence of CV Risk Factors	3,715 (75.2%)	4,822 (85.7%)	8,537 (80.8%)
Hypertension	2,409 (48.7%)	3,709 (65.9%)	6,118 (57.9%)
Hypercholesterolemia	1,940 (39.2%)	2,954 (52.5%)	4,894 (46.3%)
Diabetes Mellitus	893 (18.1%)	1,511 (26.9%)	2,404 (22.7%)
Family history of CAD	1,451 (29.4%)	1,728 (30.7%)	3,179 (30.1%)
Smoking	2,204 (44.6%)	1,621 (28.8%)	3,825 (36.2%)
Obesity	965 (19.5%)	1,295 (23.0%)	2,260 (21.4%)
Previous CVD	1,042 (21.1%)	2,672 (47.5%)	3,714 (35.1%)
Myocardial infarction	498 (10.1%)	1,462 (26.0%)	1,960 (18.5%)
Prior CABG	84 (1.7%)	534 (9.5%)	618 (5.8%)
Prior PCI	388 (7.8%)	1,170 (20.8%)	1,558 (14.7%)

CABG=coronary artery bypass graft; CAD=coronary artery disease; CV=cardiovascular; CVD=cardiovascular disease; NSTEMI=non-ST-segment elevation myocardial infarction; PCI=percutaneous coronary intervention; STEMI=ST-segment elevation myocardial infarction; UA=unstable angina

Pre-hospital management: Pre-hospital care was given to less than half of the patients, and a pre-hospital electrocardiogram (ECG) was conducted in 40% of patients. See further details below:

	STEMI (N = 4,943)	**UA/NSTEMI (N = 5,625)**	**Total (N = 10,568)**
Pre-hospital care	2,435 (49.3%)	2,303 (40.9%)	4,738 (44.8%)
Time From Symptom Onset to First Medical Attention (hours) Mean (SD)	2.749 (3.8995)	3.522 (4.4980)	3.071 (4.1762)
Pre-hospital ECG	45%	36%	40%
Any Pre-Hospital Medication	1,314 (26.6%)	849 (15.1%)	2,163 (20.5%)
Thrombolytics	107 (2.2%)	5 (0.1%)	112 (1.1%)
Antiplatelets	1,292 (26.1%)	827 (14.7%)	2,119 (20.1%)
Anticoagulants	703 (14.2)	246 (4.4)	949 (9.0%)
Antiplatelets in Patients Receiving Pre-Hospital Care			
Aspirin	52%	35%	44%
Clopidogrel	26%	9%	18%
Prasugrel	1.6%	0.3%	1.0%
Abciximab	0.8%	0%	0.4%

ECG=electrocardiogram; NSTEMI=non-ST-segment elevation myocardial infarction; SD=standard deviation; STEMI=ST-segment elevation myocardial infarction; UA=unstable angina

Inter-hospital transfer patterns: Patients were categorized as non-transferred (NT), transferred in (TI) from another hospital and then discharged, or transferred out (TO) to a second hospital but discharged from their initial hospital after transfer back. Two-thirds of ACS patients were NT, and one-third were TI or TO.

Coronary angiography (at any location) was more frequently performed in patients admitted to a hospital with a 24/7 (92%) or non-24/7 (77%) catheterization (Cath) Lab facility than in those without one (55%). The lack of on-site 24/7 Cath Lab facilities, or the availability of more advanced care, were the most frequent reasons for inter-hospital transfer.

In-hospital management: Among NSTE-ACS patients 78.7% received coronary angiography and 59.0% underwent revascularization, while 41.0% were medically managed. Among STEMI patients, 75.5% received reperfusion therapy (primary PCI or fibrinolysis).

The following table shows the use of antithrombotic drugs in the early treatment of ACS, by number of agents:

Number of Anticoagulants	**Number of Antiplatelets**			**Total**
	0-1	**2**	**3-4**	
0	357 (3.4%)	1,708 (16.2%)	203 (1.9%)	2,268 (21.6%)
1	430 (4.1%)	4,801 (45.4%)	1,091 (10.3%)	6,322 (59.8%)
2-4	46 (0.4%)	1,314 (12.4%)	618 (5.9%)	1,968 (18.6%)
Total	833 (7.9%)	7,823 (74.0%)	1,912 (18.1%)	10,568 (100%)

Specifically, the most common patterns of antiplatelets (pre- and in-hospital) were:

	STEMI (N = 4,943)	**UA/NSTEMI (N = 5,625)**	**Total (N = 10,568)**
TAP	1,222 (24.7%)	483 (8.6%)	1,705 (16.1%)
Aspirin+ clopidogrel+GP IIb/IIIa inh	1,084 (21.9%)	464 (8.2%)	1,548 (14.6%)
Aspirin+prasugrel+GP IIb/IIIa inh	138 (2.8%)	19 (0.3%)	157 (1.5%)
DAP	3,481 (70.4%)	4,463 (79.3%)	7,944 (75.2%)
Aspirin+clopidogrel	3,121 (63.1%)	4,249 (75.5%)	7,370 (69.7%)
Aspirin+prasugrel	360 (7.3%)	214 (3.8%)	574 (5.4%)
Single antiplatelet therapy	219 (4.4%)	630 (11.2%)	849 (8.0%)
Aspirin alone	140 (2.8%)	418 (7.4%)	558 (5.3%)
Clopidogrel alone	79 (1.6%)	212 (3.8%)	291 (2.8%)

DAP=dual antiplatelet therapy; inh=inhibitor; NSTEMI=non-ST-segment elevation myocardial infarction; STEMI=ST-segment elevation myocardial infarction; TAP=triple antiplatelet therapy; UA=unstable angina

Medications at discharge were:

	STEMI (N = 4,943)	UA/NSTEMI (N = 5,625)	Total (N = 10,568)
TAP	9 (0.2%)	5 (0.1%)	14 (0.1%)
Aspirin+clopidogrel+other	8 (0.2%)	4 (0.1%)	12 (0.1%)
DAP	4,627 (93.6%)	4,649 (82.6%)	9,276 (87.8%)
Aspirin+clopidogrel	4,077 (82.5%)	4,395 /78.1%)	8,472 (80.2%)
Aspirin+prasugrel	520 (10.5%)	229 (4.1%)	749 (7.1%)
Single antiplatelet therapy	279 (5.6%)	856 (15.2%)	1135 (10.7%)
Aspirin alone	199 (4.0%)	700 (12.4%)	899 (8.5%)
Clopidogrel alone	78 (1.6%)	148 (2.6%)	226 (2.1%)
No antiplatelets	17 (0.3%)	95 (1.7%)	112 (1.1%)

DAP=dual antiplatelet therapy; NSTEMI=non-ST-segment elevation myocardial infarction; STEMI=ST-segment elevation myocardial infarction; TAP=triple antiplatelet therapy; UA=unstable angina

In-hospital bleeding and ischemic events: A total of 3.25% of patients experienced non-fatal in-hospital bleeding events. There was a significant association between the increasing number of total antithrombotic drugs and risk of total non-fatal in-hospital bleeding episodes ($p<0.001$).

A total of 2.33% of patients experienced at least 1 ischemic event. No significant association was found between total number of antithrombotic drugs and incidence of in-hospital ischemic events.

In-hospital use of healthcare resources: The following table shows some key determinants of use of healthcare resources, which tended to be slightly higher in patients without CVD (-CVD) than in patients with CVD (+CVD).

	STEMI (N = 4,899)		NSTE-ACS (N = 5,576)	
	+CVD (n = 1,042)	**-CVD (n = 3,857)**	**+CVD (n= 2,672)**	**-CVD (n = 2,904)**
Any cardiac catheterization, %	84.3	86.5	73.1	82.8
Any PCI/PCI+≥1 stent, %	74.0/67.0	78.0/75.8	48.1/44.2	61.2/59.5
Length of hospital stay, median (IQR), days	7 (5–9)	6 (5–9)	6 (5–10)	6 (4–8)

ACS=acute coronary syndrome; CVD=cardiovascular disease; IQR=interquartile range; NSTE=non-ST-segment elevation; PCI=percutaneous coronary intervention; STEMI=ST-segment elevation myocardial infarction

Post-Discharge Data (Follow-Up Phase)

Availability of short-term and long-term follow-up results: Collection of information through telephone call interviews was possible in the vast majority of cases. A summary of the contact information is presented below:

	STEMI (N = 4,943)	UA/NSTEMI (N = 5,625)	Total (N = 10,568)
Number of Patients with Follow-Up Information (from Patient or Relative) Up to 6 Months	4,637 (93.81%)	5,183 (92.14%)	9,820 (92.92%)
Number of Patients with Follow-Up Information (from Patient or Relative) Up to 2 Years	4,635 (93.77%)	5,184 (92.16%)	9,819 (92.91%)

NSTEMI=non-ST-segment elevation myocardial infarction; STEMI=ST-segment elevation myocardial infarction; UA=unstable angina

Outcomes during follow-up: The table below shows the number of patients with CV events, bleeding events, and mortality, respectively, during the 2 years of follow-up:

	STEMI (N = 4,943)	UA/NSTEMI (N = 5,625)	Total (N = 10,568)
Incidence of CV Event			
Discharge to 6 months	375 (7.59%)	544 (9.67%)	919 (8.70%)
Discharge to 1 year	488 (9.87%)	735 (13.07%)	1,223 (11.57%)
Discharge to 2 years	638 (12.91%)	960 (17.07%)	1,598 (15.12%)
Incidence of bleeding Event			
Discharge to 6 months	78 (1.58%)	108 (1.92%)	186 (1.76%)
Discharge to 1 year	108 (2.18%)	163 (2.90%)	271 (2.56%)
Discharge to 2 years	154 (3.12%)	209 (3.72%)	363 (3.43%)
Mortality rate			
Discharge to 6 months	108 (2.18%)	175 (3.11%)	283 (2.68%)
Discharge to 1 year	155 (3.14%)	251 (4.46%)	406 (3.84%)
Discharge to 2 years	227 (4.59%)	382 (6.79%)	609 (5.76%)

CV=cardiovascular; NSTE=non-ST-segment elevation; STEMI=ST-segment elevation myocardial infarction; UA=unstable angina

Medication during follow-up: Of patients discharged on dual antiplatelet therapy (DAT) who completed follow-up and did not die during the course of the study (n=8,890), 91.7%, 82.9%, 63.6%, and 61.9% remained on DAT at 6, 12, 21, and 23 months, respectively.

In the case of patients on aspirin+clopidogrel (n=8,132), the corresponding percentages were 91.5%, 83.1%, 64.4%, and 62.8%, at 6, 12, 21, and 23 months, respectively.

In the case of patients on aspirin+prasugrel (n=735), the corresponding percentages were 93.5%, 80.4%, 53.2%, and 51.5%, at 6, 12, 21, and 23 months, respectively.