STUDY REPORT SYNOPSIS

TOURACO Study: Long-Term Follow-Up and management patterns of patients with Acute Coronary Syndrome in Middle East and Africa

Non-interventional study , Descriptive, epidemiological, observational, multinational, multicenter prospective and longitudinal cohort study

Milestones:

• First approval from the Ethics Committee	13-Dec-2015*
• Date of first patient information visit	28-Dec-2015
• Date of last patient information visit	02-Apr-2020
• Data review meeting	15-Sep-2020
• Data base lock	26-Nov-2020
• Final statistical analysis report	10-Dec-2020
• Clinical study report	28-Mar-2021

*see **Appendix 3** for all approval dates

Phase of development: Non-interventional study

Sponsor: [redacted]

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This study was performed in compliance with Good Clinical Practice (GCP) and Good Pharmacoepidemiology Practice (GPP), including the archiving of essential documents.

Study Centre(s)	46 community and university hospitals, from the public and the private sector, with cardiac intervention facilities and regional and community-type hospitals that have limited (if at all) cardiac intervention facilities in Algeria, Bahrain, Egypt, Kuwait, Oman, Qatar, Saudi Arabia, and United Arab Emirates Number of active centres: 45
Study period	Prospective data of patients included between 28/12/2015 and 14/02/2017 and followed up until 02/04/2020.
Study objectives and endpoints	Main objective and endpoint were: 1. To evaluate the quality of care by assessing the treatment patterns of acute coronary syndrome (ACS) at one month of follow-up, in a real-life setting for patients hospitalized with an ACS (i.e. ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), unstable angina (UA)), against international guidelines (ESC or ACC guidelines) or against local guidelines when the international one are not applicable. o Antithrombotic, antihypertensive, diabetic lowering and cholesterol lowering agents' prescription at one month of follow-up after discharge from hospital. Secondary objectives and endpoints: 1. To evaluate the quality of care by assessing the treatment patterns of acute coronary syndrome at discharge from hospital and at 6 months, 1, 2 and 3 years, in a real-life setting for patients hospitalized with an ACS (i.e. STEMI, NSTEMI, unstable angina), against what is recommended in the local guidelines. o Antithrombotic, antihypertensive, diabetic lowering and cholesterol lowering agents' prescription at intra-hospital period (from the first contact till discharge), 6 months, 12, 24 and 36 months of follow-up. 2. To describe the level of control of the different ACS related risk factors (diabetes, hypertension, dyslipidaemia), in a real-life setting for patients hospitalized with an ACS (i.e. STEMI, NSTEMI, unstable angina) at discharge from hospital and at 6 months. The level of control is described in terms of the frequency of antithrombotic, antihypertensive, diabetic lowering and cholesterol lowering agents' prescription, and in terms of blood tests and PE assessments.

	○ Level of control of ACS risk factors (diabetes, HT and dyslipidaemia) at intra-hospital period (from the first contact till discharge), and at 6 months of follow-up. At 12, 24 et 36 months, the level will be measure if the patient come for a planned visit (OPTIONNAL). ○ Deviation of the treatment patterns of ACS against what is recommended in the local guidelines for the management of ACS at the different time intervals. ○ Medication interruptions and main causes.
Study design	Descriptive, non-interventional, multinational, multicentre, prospective, and longitudinal cohort study, conducted in community and university hospitals, from the public and the private sectors in Algeria, Bahrain, Egypt, Kuwait, Oman, Qatar, Kingdom of Saudi Arabia (KSA), and the United Arab Emirates (UAE).
Setting	The study collected information on the characteristics and the management of patients hospitalized for ACS within 24 hours of symptom onset and who have a final diagnosis of UA, STEMI or NSTEMI. Patients underwent clinical assessments and received the standard medical care as determined by the treating physician. Patients did not receive experimental intervention or experimental treatment as a consequence of their participation in this observational study. In addition, the study intended to collect data on patients diagnosed with UA, STEMI or NSTEMI under conditions of routine clinical care. The data for this observational study were collected on paper or electronic case report forms (paper CRF/eCRF). Patient's visits occurred at inclusion, at discharge visit, 1 and 6 months after discharge. The follow-up 1, 2 and 3 years after discharge were optional and were performed over the phone or during a planned face to face visit, and data for statistical analysis were recorded accordingly. The long -term follow-up was considered as the time from hospital discharge up to 3 years after the index event.
Selection Criteria of Subjects	<u>Inclusion criteria:</u> Patients presenting to the emergency room (or equivalent) and diagnosed with UA, STEMI or NSTEMI were eligible to participate if all the following criteria applied: 1. Provision of subject informed consent. 2. Provision of the Contact Order Form. 3. Female and/or male aged 21 years and over. 4. Diagnosis of STEMI, NSTEMI or UA using the following definitions:

	Criteria for STEMI diagnosis[1]: (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 left bundle branch block (LBBB) 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[2]: (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[2]: (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 ischemia by non-invasive imaging or significant coronary stenosis (at angiography). 5. Hospitalized within 24 hours of onset of symptoms during the current episode* or transferred from another hospital within 24 hours of the onset of symptoms**. * In case of intermittent symptoms, the symptoms onset is that of the last episode ** If the referred hospital can get the initial data of the patient from the transferring hospital, transferring period is not considered as a limitation for patient initiation <u>Exclusion criteria:</u> Patients were not be eligible to participate if any of the following exclusion criteria were present: 1. UA, STEMI and NSTEMI precipitated by or as a complication of surgery, trauma, or gastrointestinal bleeding or post-PCI. 2. UA, STEMI and NSTEMI occurring in patients already hospitalized 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 (i.e. tourist, non-native speaker or did not understand the local language, psychiatric disturbances). 4. Already included in TOURACO study by another centre/investigator. 5. Presence of serious/severe co-morbidities in the opinion of the Investigator which could have limited short-term (i.e., 6 months) life expectancy. 6. If participating in any interventional clinical trial, should have been adapted to each country local regulation. 7. Patients with any psychotic disorders. 8. Pregnancy.
Study Population and Size	No formal sample size calculation was performed. It was assumed that each MENA region was to include 300 patients, except for Algeria recruiting 200 patients.
Variables and data sources	Data relative to patients and site questionnaires were collected using paper and electronic case report form (CRF).
Statistical Methods	Statistical analysis was performed using SAS software SAS 9.4 and SAS/STAT 15.1. Depending on criterion's nature, standard descriptive statistics were used. Furthermore, for qualitative variables, the 2-sided 95% confidence interval (CI) was calculated for the main modality using an asymptotic method. Normality of distributions were tested using Kolmogorov-Smirnov tests and visually checked, if normality of distributions was rejected the quantitative variables were categorized using quartiles. All statistical tests were two-sided, and the statistically significant threshold was set at 5%. No adjustment of risk alpha was done as this is an observational study where all analyses were exploratory. Otherwise specified, data were summarized per country and overall. Data up to discharge were also summarized by ACS type. Otherwise specified, all analyses on in-hospital period and until hospital discharge were performed on the full analysis set (FAS) and all follow-up population (FUP) data were summarized on the follow-up population. All other analyses were performed on the FUP. Survival analysis was performed using Kaplan Meier method. Also, the total number of deaths during the study was displayed in each country and overall.

	As date of medical event was unknown, the probability of occurrence of a medical event was estimated on the FUP population, using an actuarial estimator at specific time intervals and displayed with the 2-sided 95% CI. Patients lost-to-follow-up were censored at the time of last news.
Results	Site disposition Overall, 46 centres accepted to participate to the study and 45 (97.8%) included at least 1 patient. Most of the centres were equipped with a cathlab [40 (87.0%) centres], a coronary care unit [43 (93.5%) centres], and/or a 24/7 primary percutaneous coronary intervention (PCI) program [36 (78.3%) centres]. Only 18 (39.1%) centres had a cardiac surgery availability. Patient disposition Overall, 1 117 (93.7%) patients were included in the follow-up population. Most patients were males [927 (82%)]. Median age was 56 [49; 64] years and BMI was 28.1 [25.1; 31.6] kg/m². At arrival at the hospital, 659 (58.3%) had a Killip class I, 114 (10.1%) patients a Killip class II, 30 (2.7%) patients a Killip class III and 9 (0.8%) patients a Killip class IV. Killip classification was not applicable for 319 (28.2%) patients. Concerning the risk factors, 490 (43.4%) patients were current smokers and 140 (12.4%) were former smokers; 582 (51.5%) patients had hypertension; 381 (33.7%) patients had hypercholesterolemia; 203 (18%) had a history of coronary heart disease and 449 (39.7%) patients had type 2 diabetes. Among the diabetic patients, 287 (60.4%) were treated with an oral anti-diabetic agent. Initial patient care Overall, it took 165 [69; 343] minutes between symptom onset and the first medical contact and 1 048 (92.7%) patients did not call an emergency ambulance. The delay between symptoms onset and the arrival to the hospital was 180 [90; 388] minutes. For 1 025 (90.6%) patients, arrival was at the emergency room. An electrocardiogram (ECG) was performed in 1 091 (96.5%) patients within 185 [90; 360] minutes of symptom onset: 1 058 (97.1%) patients had a sinus rhythm, and 27 (2.5%) patients had a complete arrhythmia due to atrial fibrillation/flutter. There were no intraventricular conduction disorders for 1 027 (94.2%) patients; 1 073 (98.4%) patients did not present atrioventricular block AVB III. Diagnosis at arrival was ACS with ST elevation for 581 (51.4%) patients and ACS without ST elevation for 530 (46.9%) patients. ACS types were STEMI for 602 (53%) patients, NSTEMI for 306 (27%) patients and UA for 223 (20%) patients.

	The current episode was not an inaugural event for 250 (22.1%) patients; 199 (79.6%) patients had a history of angina and 122 (48.8%) patients a history of myocardial infarction (last episode 4 [1; 8] years ago). Anti-hypertensive agents were prescribed to 775 (68.6%) patients, anti-diabetic agents (oral and insulin) were prescribed to 484 (42.8%) patients and cholesterol lowering agents to 1 076 (95.2%) patients. Initial left ventricular ejection function (LVEF) was 50 [40; 58]% and was assessed by echography for 1 018 (90.1%) patients and a coronarography was performed for 980 (86.8%) patients. Coronarography was performed after transfer for 558 (56.9%) patients. Anti GPIIb-IIIa was used for 190 (19.4%) patients. Access was femoral for 400 (40.8%) patients and radial for 580 (59.2%) patients. Coronarography was abnormal for 942 (96.1%) patients. TIMI grade flow score was 0 for 184 (19%) patients, 1 for 144 (15%) patients, 2 for 208 (21%) patients, 3 for 312 (32%) patients and not applicable for 123 (13%) patients. An angioplasty was attempted in 765 (67.8%) patients: 281 (37%) received Everolimus, 131 (17%) patients Sirolimus, 15 (2%) patients Paclitaxel and 335 (44%) patients another type of stent. Angioplasty occurred after transfer for 423 (55.3%) patients. A thrombo-aspiration occurred in 79 (10.3%) patients and post-conditioning manoeuvre in 122 (16.0%) patients. Final TIMI score was 3 for 668 (87%) patients. According to TIMI criteria, a minor haemorrhage occurred in 20 (1.8%) patients and a major in 17 (1.5%) patients. Haemorrhage occurred after cardiac surgery in 22/37 (59.5%) patients. <u>Hospitalization</u> During hospitalization, maximal Killip class was 1 for 716 (63%) patients. Only 24 (2.1%) patients presented an ischemic relapse with ECG signs without necrosis, 8 (0.7%) patients a necrosis relapse and 4 (0.4%) patients a stent thrombosis. An echocardiography was performed for 966 (95.7%) patients, a coronarography for 833 (82.6%) patients and a coronary angioplasty for 686 (68.3%) patients. Overall, 43 (3.8%) patients required another surgery during hospitalization. Throughout the hospitalization period, 10 (0.9%) patients died: 3 (30%) patients died of sudden death presumed to be cardiac, 1 (10%) patient died of heart failure, 3 (30%) patients died of a heart rhythm disorder, 1 (10%) patient died of another cardiovascular disorder and 2 (20%) patients died from a cause other than cardiovascular disorder. Death occurred 4 [1; 8] days after current episode symptom’s onset.

	Hospital discharge Patients were discharged 4 [2; 6] days after symptom's onset and 1 093 (97.1%) patients went home. ECG was sinusal for 1 053 (93.5%) patients or presented a complete arrhythmia/auricular fibrillation for 15 (1.3%) patients. A Q-wave was detected on 395 (35.1%) patient's ECGs. LVEF at discharge was normal for 456 (40%) patients, mildly altered for 199 (18%) patients, moderately altered for 124 (11%) patient and significantly altered for 43 (4%) patients. LVEF at discharge was unknown for 304 (27%) patients. LVEF was measured by echography for 820 (72.8%) patients. Method was unknown for 302 (26.8%) patients. Left ventricular end-diastolic diameter (LVEDD) measured on 534 patients (n missing= 597), was 50 [44.0; 54.0] mm. Left ventricular end-systolic diameter (LVESD) measured on 518 patients (n missing = 613), was 34 [27.0; 39.0] mm. Follow-up During the follow-up period, information was mainly provided by the patient him/herself. Contact was predominantly by phone. End of the study occurred before 3 years for 235 (20.8%) patients. Reasons for early discontinuation were death for 64 (27.2%) patients, consent withdrawal for 2 (0.9%) patients and lost to follow-up for 169 (71.9%) patients. Overall, 72 (6.4%) patients died during the study including 10 patients during hospitalization. Cumulative mortality rate was 1.7 ±0.4% at 1 month, 3.8±0.6% at 1 year, 5.1±0.7% at 2-year and 6.2±0.7% at 3-years. Cumulative mortality rate in males was 0.6 ±0.2% at 1 month, 2.8±0.6% at 1 year, 3.9±0.7% at 2-year and 4.5±0.7% at 3-years. Probability of a thrombo-embolic event was 1.5 ±0.4% during the 1st month, 1.9% ±0.4% during 1-month and 6-month, 3.1 ±0.5% during 6-month and 1-year, 4.1 ±0.6% during 1-year and 2-year and 6.6 ±0.9% during 2-year and 3-year. Probability of a medical procedure was 6.1 ±0.7% at 1-month, 8.9 ±0.9% during 1-month and 6-month, 14.5 ±1.1% during 6-month and 1-year, 18.5 ±1.2% during 1-year and 2-year and 26.6 ±1.7% during 2-year and 3-year. Probability of a hospitalization was 7.6±0.8% during the 1st month, 10.6 ±0.9% during 1-month and 6-month, 15.9 ±1.1% during 6-month and 1-year, 20.8 ±1.3% during 1-year and 2-year and 29.9 ±1.7% during 2-year and 3-year. During the study, few patients interrupted their treatments prescribed at discharge: 20 (2.0%; data missing=107) patients during the 1-month period 5 (1.1%; data missing=653) patients during the 6-month period, 32 (3.7%; data missing=247) patients within the 1st year, 46 (5.7%; data missing=311)

	patients during the 2nd year and 90 (10.1%; data missing=225) patients during the 3rd year. The main objective of the TOURACO study was the compliance of treatment, with guidelines, at 1 month of follow-up. At 1 month, among patients with a known treatment, compliance with guidelines was good in 723 (78.6%) patients and poor 197 (21.4%) patients (n missing=197). Compliance was good for 306 (74%) patients (n missing =702) at 6 months, for 473 (77%) at 1 year (n missing=503), for 301 (72.5%) at 2 years (n missing= 702) and for 379 (64.9%) at 3 years (n missing= 533).
[redacted]	[redacted]