STUDY REPORT SYNOPSIS (ABSTRACT)

Long-tErm follow-uP of antithrombotIc management patterns In Acute CORonary Syndrome patients in Asia-China Extension

Background/Rationale:

The choice of anti-thrombotic therapies and strategies is continuously evolving as well as to the international guidelines for their use. The available data concerning the efficacy, safety and treatment compliance of specific antithrombotic therapies and strategies and combinations in ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation acute coronary syndrome (NSTE-ACS) patients is derived, essentially from clinical trials and is generally available only up to 12 months after the index event. Data of antithrombotic management patterns (AMPs) on healthcare resource utilization beyond 2 years after acute coronary syndrome (ACS) are limited but important.

Although the economic burden of myocardial infarction (MI) is highest in the first year after the event, the complications of MI beyond 2 years also exert a burden on the economy, driven by both hospitalisations and medications. Few such data are available in patients with history of ACS. Data of the associated costs for the recurrent events would provide additional important information from a payer perspective. Improving understanding of the long-term management and outcomes of patients with prior ACS is paramount for reducing the disease burden.

The selection of patients in clinical trials is tailored and focused on a specific patient cohort, and procedures to be followed are imposed by the trial protocol. There is a drawback that neither the patient cohort nor the procedures implemented for clinical trials are reflective of all patients seen and medical treatments applied in every day clinical practice. In addition, the more critically ill and vulnerable patients (for example: the elderly, high risk patients and patients with multiple co-morbidities) are frequently excluded from clinical trials, so valuable data concerning this patient population is lacking. Therefore, it is very important to collect related data in a “real-life” setting for patients.

Although TIGRIS study was previously designed to collect real world evidence data in stable coronary artery disease (CAD) patients, describing burden of disease, unmet medical needs, healthcare resource utilization were needed in support of PEGASUS study for stable CAD patients. The baseline characteristics data might be missing for TIGRIS study, while EPICOR Asia had collected first hand data from patient’s hospitalization of index event up to 2 years. Therefore, EPICOR Asia-China Extension compared the longer-term management and

outcomes of patients between acute-setting and 5 years later, as an additional support for PEGASUS study. Secondly, there was no similar study in China so far.

Objectives and hypotheses:

a) Primary objective

To describe the long-term (3 to 5 years after the ACS index event) AMPs in a "real-life" setting for patients hospitalized with an ACS [i.e. STEMI, Non-ST-segment Elevation Myocardial Infarction (NSTEMI), Unstable Angina (UA)] in China.

b) Secondary objectives

1. To describe the impact of AMPs on clinical outcomes, healthcare resource use and quality of life (QoL) in a "real-life" setting.

2. To describe the variations in AMPs for patients with a history of ACS and the clinical outcomes (ischemic and bleeding) after 2 years following the index event until 5 years.

3. To estimate the ACS associated health care resource consumption and related costs after 2 years following the index event until 5 years. In addition, to describe the components of resource consumption (i.e. long-term health care resource use of the specific disease managements, including hospital stay, medical transportation, medical treatments and procedures, visits to any health care provider, and healthcare resource use related to the disease outcomes and treatment-associated events).

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

5. To evaluate the impact of specific clinical and non-clinical events in the 3 year follow-up period (e.g. bleeds, planned and non-planned medical interventions) on antithrombotic treatment interruptions, and on the occurrence of subsequent thromboembolic events.

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

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

Methods:

Study design

EPICOR Asia-China Extension was a multi-centre, observational, longitudinal cohort study which included part of Chinese patients from EPICOR Asia study. The follow-up period was 3 years.

Number of study sites in this study

This study was planned to be conducted in approximately 50 sites. Actually, 49 sites were involved.

Number of patients in this study

This study was planned to enrol approximately 3,000 patients. Actually, 2,334 patients were enrolled.

Countries

China

Target patient population

Patient population was part of the Chinese patients from EPICOR Asia study, and these patients had completed the EPICOR Asia study.

Patients were eligible to participate in this study if they satisfied all the following criteria:

1. Written informed consent was provided.
2. Contact Order Form was provided.
3. Aged 18 years or older.
4. Enrolled in EPICOR Asia study and completed the 2 year follow-up.

Patients were ineligible to participate in this study if they satisfied any of the following exclusion criteria:

1. 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 could not understand the local language, psychiatric disturbances, alcohol or drug abuse).
2. Already included in the EPICOR Asia-China Extension observational study.
3. Presence of serious/severe co-morbidities in the opinion of the investigator which might limit short term (i.e. 6 month) life expectancy.
4. Current participation in an interventional clinical trial.
5. Patients receiving Ticagrelor beyond 12 months and other off-label use.

Study duration per patient

36 months

Study variables

a) Primary variables:

1. AMPs of STEMI and NSTEMI/UA.
2. Clinical events (deaths from vascular causes, MI, stroke and bleeding events).

b) Other variables:

1. Patient characteristics.
2. Event characteristics.
3. Clinical management; pharmacological treatment and diagnostic/invasive procedures.
4. Treatment associated bleeding (type and severity).
5. AMP interruptions and main causes.
6. QoL based on the European Quality of Life-5 Dimensions Questionnaire (EQ-5D, an instrument for measuring QoL).
7. Consumption of health resources.

Statistical methods

Statistical methods appropriate for epidemiological studies were used to analyse the collected data.

A statistical analysis plan (SAP) was prepared and finalized before interim analysis. The final statistical analysis was conducted based on the protocol version 1.0 (19 Sep, 2014), the SAP version 1.0 (15 Nov, 2016), and the database locked on 17 Jul, 2018. Notes: the database was originally locked on 30 Oct, 2017. However, 111 events entered into CRF were found not to be submitted to the event committee for review, and 17 events submitted to the event committee for review were found not to be entered into CRF. Therefore, the database was reopened in 10 Apr, 2018 and relocked on 17 Jul, 2018.

Of note, the compliance with the international guidelines for AMP use was not determined in this analysis.

Descriptive statistics included non-missing patients (n), mean, median, standard deviation (SD), minimum (min) and maximum (max) for continuous variables, as well as n, frequency and percentage for categorical values.

For the population estimation of the variables, the two-sided 95% confidence interval (CI) were obtained if considered relevant.

AMPs were grouped after taking into account only the different treatment options shown by the descriptive analysis.

The Kaplan-Meier method was utilized to calculate and plot the cumulative incidences of the first occurrence of clinical outcomes (deaths from vascular causes, MI, stroke and bleeding events) at 3, 4 and 5 years.

A descriptive analysis was performed to assess the factors related with healthcare resources consumption. Cumulative costs (per patient) associated with hospitalization/event were investigated.

Determination of sample size

Assuming a 5-year event rate of around 20-30%, a sample size of 3,000 patients allowed describing an expected event rate for the clinical outcomes (deaths, thrombo-embolic events, and bleeding events) between 20% and 30% with a two-sided 95%CI that extended in ± 1.4% and ± 1.6% from the observed proportion, respectively.

Results:

Disposition of patients

A total of 2,334 patients were enrolled from 49 sites in this study, and none of them was excluded from full analysis set (FAS). Among the 2,334 patients, 2,093 patients (89.7%) completed the study, i.e. they completed 5-year visit and had all the information required at the last visit. Among the 2,334 patients, 241 patients (10.3%) discontinued from the study, and the main reasons were being lost to follow-up (58.1%), death (27.0%) and voluntary discontinuation (11.2%).

Subgroups

Among the 2,334 patients, when patients were classified into subgroups by their final ACS diagnosis, 1,160 patients (49.7%) were classified into STEMI subgroup, 343 patients (14.7%) were classified into NSTEMI subgroup, and 831 patients (35.6%) were classified into UA subgroup. Among the 2,334 patients, considering whether the patient had percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) during the hospitalisation for the index event in EPICOR Asia study, 1,846 patients (79.1%) were classified into invasive subgroup, and 488 patients (20.9%) were classified into non-invasive subgroup. Among the 2,334 patients, considering the AMPs at 2 years after the ACS index event, 143 patients (6.1%) were classified into 0 AP subgroup, 1,690 patients (72.4%) were classified into 1 AP subgroup, and 501 patients (21.5%) were classified into 2+ AP subgroup (AP: antiplatelet; 2+ AP: 2 or more APs).

Primary variables - AMPs

AMPs at each visit

For all the FAS patients (2,334 patients) at 2 years after the ACS index event, 143 patients (6.1%) were treated without any AP. A total of 1,690 patients (72.4%) were treated with only 1 AP, including 1,597 patients (68.4%) received aspirin only, 92 patients (3.9%) received clopidogrel only and 1 patient received cilostazol only. A total of 501 patients (21.5%) were treated with 2+ APs, including 495 patients (21.2%) with aspirin+clopidogrel, 2 patients (0.1%) with aspirin+ticagrelor, 2 patients (0.1%) with cilostazol+clopidogrel, 1 patient with aspirin+cilostazol and 1 patient with bufferin+clopidogrel. These results and the results for all the patients at 2.5, 3, 3.5, 4, 4.5 and 5 years after the ACS index event indicated that majority of the FAS patients were treated with only 1 AP (mainly aspirin) from 2 to 5 years after the ACS index event.

AMPs in subgroups

For the patients at 2 years after the ACS index event, a numerically lower proportion of patients in NSTEMI subgroup (66.8%, 229/343) were treated with 1 AP than those in STEMI (73.5%, 853/1,160) and UA subgroups (73.2%, 608/831), respectively. A numerically higher proportion of patients in NSTEMI subgroup (28.9%, 99/343) were treated with 2+ APs than those in STEMI (20.7%, 240/1,160) and UA subgroups (19.5%, 162/831), respectively. A numerically higher proportion of patients in invasive subgroup (22.9%, 423/1,846) were treated with 2+ APs than that in non-invasive subgroup (16.0%, 78/488). These results and the results for the patients at 2.5, 3, 3.5, 4, 4.5 and 5 years after the ACS index event indicated that during 2-5 years after the ACS index event: (1) the proportion of patients treated with 1 AP in NSTEMI subgroup was numerically lower than STEMI and UA subgroups; (2) the proportion of patients treated with 2+ AP in NSTEMI subgroup was numerically higher than STEMI and UA subgroups; (3) the proportion of patients treated with 2+ AP in invasive subgroup was numerically higher than non-invasive subgroup.

Changes of AMPs from baseline

Among patients in FAS, some patients had their AMPs changed from baseline, and the proportion increased along with the follow-up years (2.5 years: 6.5%, 3 years: 8.7%, 3.5 years: 12.9%, 4 years: 16.0%, 4.5 years: 18.6%, 5 years: 19.3%).

In 0 AP subgroup, 138 (5.9%), 137 (5.9%), 130 (5.6%), 123 (5.3%), 119 (5.2%) and 116 (5.1%) patients remained in the same treatment subgroup at 2.5, 3, 3.5, 4, 4.5 and 5 years after the ACS index event, respectively. In 1 AP subgroup, these numbers were 1608 (68.9%), 1580 (67.7%), 1537 (65.9%), 1485 (64.0%), 1427 (62.3%) and 1402 (62.0%), respectively. In 2+ AP subgroup, these numbers were 437 (18.7%), 413 (17.7%), 365 (15.6%), 340 (14.7%), 318 (13.9%) and 309 (13.7%), respectively.

Considering the AMP changes by subgroups at 5 years after the ACS index event, NSTEMI subgroup had a higher rate of AMP change [23.8%, 78/328; (3+0+24+13+11+27)/328] comparing to STEMI subgroup [19.4%, 219/1,128; (11+3+89+34+13+69)/1,128] and UA subgroup [17.2%, 139/807; (5+1+47+26+8+52)/807]. The rates of AMP change in invasive

subgroup [19.2%, 345/1,796; (11+4+116+62+23+129)/1,796] and non-invasive subgroup [19.5%, 91/467; (8+0+44+11+9+19)/467] were similar.

Primary variables - predefined clinical events

Cumulative incidence rates of the composite event of all-cause mortality, MI and stroke - FAS

Among the 2,334 patients, 227 patients (9.7%) had 286 composite clinical events of all-cause mortality, MI and stroke in the study. Among the 2,334 patients, 65 patients (2.8%) died from all causes, including 32 patients (1.4%) due to vascular cause. Among the 2,334 patients, 105 patients (4.5%) suffered from MI, and the number of MI events was 120. Among the 2,334 patients, 88 patients (3.8%) had 101 stroke events, including 73 patients (3.1%) with 83 ischemic stroke, 9 patients (0.4%) with 10 hemorrhagic stroke and 8 patients (0.3%) with unknown type of strokes.

Cumulative incidence rates of the composite event of all-cause mortality, MI and stroke - 0 AP, 1 AP, and 2+ AP subgroups

In this study, the cumulative incidence rate of the composite event of all-cause mortality, MI and stroke was slightly higher in 2+ AP subgroup (13.2%, 66/501) than 0 AP subgroup (10.5%, 15/143) and 1 AP subgroup (8.6%, 146/1,690).

Cumulative incidence rates of the composite event of all-cause mortality, MI and stroke - STEMI, NSTEMI, and UA subgroups

In this study, the cumulative incidence rate of the composite of all-cause mortality, MI and stroke was slightly higher in NSTEMI subgroup (12.2%, 42/343) than STEMI subgroup (8.8%, 102/1,160) and UA subgroup (10.0%, 83/831).

Cumulative incidence rates of the composite event of all-cause mortality, MI and stroke - invasive and non-invasive subgroups

In this study, the cumulative incidence rate of the composite of all-cause mortality, MI and stroke was slightly higher in non-invasive subgroup (11.5%, 56/488) than invasive subgroup (9.3%, 171/1,846).

Incidence rates of the predefined clinical events - death

Among the 2,334 patients, 65 patients (2.8%) died in the study. The main reason leading to death was cardiovascular and cerebrovascular events (47.7%, 31/65).

Incidence rates of the predefined clinical events - MI

Among the 2,334 patients, 105 patients (4.5%) had 120 MI events in the study. Among the 120 MI events, 35 MI (37.2%) were STEMI, 59 MI (62.8%) were NSTEMI and 26 missing; 117 MI events (97.5%) led to hospitalization; 55 events (45.8%) led to outpatient visit. The cumulative

incidence rate of MI events was numerically higher in 2+ AP subgroup (7.8%, 39/501) than the rates in 1 AP subgroup (3.6%, 61/1,690) and 0 AP subgroup (3.5%, 5/143).

Incidence rates of the predefined clinical events - stroke

Among the 2,334 patients, 88 patients (3.8%) had 101 stroke events in the study. Among the 101 stroke events, 83 events (89.2%) were diagnosed as ischemic stroke; 91 events (90.1%) led to hospitalization; 46 events (45.5%) led to outpatient visit.

Incidence rates of the predefined clinical events - bleeding

Among the 2,334 patients, 214 patients (9.2%) reported 290 bleeding events in the study. Among the 290 bleeding events, 47 events (22.0%) were gastrointestinal bleeding; 271 events (93.4%) were minor bleeding; 84 events (29.0%) led to hospitalization, and 155 events (53.4%) led to outpatient visit.

The cumulative incidence rate of bleeding events was numerically higher in 2+ AP subgroup (11.8%, 59/501) than the rates in 1 AP subgroup (8.3%, 140/1,690) and 0 AP subgroup (10.5%, 15/143).

Other variables - outpatient visit

In the study, 2,063 patients (88.3%, 2,063/2,334) had outpatient visits. The mean number of outpatient visits per year was 8.63, with median 6.02, min 0.3 and max 116.7. Cardiovascular specialists were most frequently visited.

Patients in NSTEMI subgroup (mean: 11.01 visits per year) visited doctors more frequently than the patients in STEMI subgroup (mean: 8.38 visits per year) and UA subgroup (mean: 7.95 visits per year). The proportion of patients with outpatient visit in invasive subgroup (90.1%, 1,663/1,846) was numerically higher than that in non-invasive subgroup (82%, 400/488). The proportion of patients with outpatient visit was numerically higher in the subgroup with more APs (76.9%, 110/143; 87.9%, 1,485/1,690; 93.4%, 468/501), and the frequency of outpatient visits has the similar results with proportion (mean: 6.90, 8.41 and 9.73 visits per year), too.

Other variables – surgery of outpatient visit

In the study, 276 patients (13.3%, 276/2,071) had surgeries during outpatient visits, and 81.2% (224/276) of these subjects had tooth extraction. The mean number of surgery per year was 0.48, with median 0.33, min 0.3 and max 3.4.

Other variables - hospitalization

In the study, 1,023 patients (43.8%, 1,023/2,334) experienced hospitalization. The mean number of hospitalization per year was 0.64, with median 0.34, min 0.3 and max 8.6. The most main reason for hospitalization was cardiovascular events (44.8%, 838/1,871). Cardiovascular events leading to hospitalization were mainly diagnosed as CAD (72.9%, 611/838). Among these CAD events, 251 events (41.1%, 251/611) were UA.

The proportion of patients with hospitalization in 2+ AP subgroup (54.5%, 273/501) was numerically higher than those in 1 AP (41.0%, 693/1,690) and 0 AP subgroups (39.9%, 57/143). In 1 AP and 2+ AP subgroups, the proportions of emergency admission were higher and the reason of hospitalization was more likely to be cardiovascular events in comparison with 0 AP subgroup. Among the patients with hospitalization during the study, the proportion of patients underwent a surgery in 2+ AP subgroup (53.0%, 141/266) was numerically higher than those in 1 AP (37.9%, 256/675) and 0 AP subgroups (38.6%, 22/57).

Other variables - cost of outpatient visit and hospitalization

As for the cost of outpatient visits of 2,034 patients without missing value, the mean total cost of treatment per year in the entire study was 6,270.84 RMB, with median 4,687.54 RMB, min 20.0 RMB and max 202,789.5 RMB. Among the total cost of treatment, cost of medication accounted for the major proportion. The mean cost of medication per year in the entire study was 6,034.77 RMB, with median 4,557.31 RMB, min 20.0 RMB and max 135,462.3 RMB. Among the 2,334 patients, 2,035 patients (87.2%) had medication cost, 915patients (39.2%) had inspection charge, and 86 patients (3.7%) had operation charge during outpatient visits. The total cost of treatment in outpatient visits was afforded by medical insurance and the patient him/herself half-to-half throughout the study. Only 33 patients had commercial insurance payment.

As for the hospitalization of 729 patients without missing value, the mean total cost of treatment per year in the entire study was 9,686.19 RMB, with median 4,457.95 RMB, min 66.4 RMB and max 221,854.3 RMB. Considering the median of cost, medication cost accounted for the biggest proportion, inspection charge took the second place, and operation charge accounted for the smallest proportion. Considering the mean of cost, medication cost accounted for the biggest proportion, operation charge took the second place, and inspection charge accounted for the smallest proportion.

Statement

Caution is required when interpreting results of observational studies, given the lack of randomization and subsequent biases (e.g. channeling bias) introduced in an observational design.

Conclusion:

Majority of the FAS patients were treated with only 1 AP (mainly aspirin) from 2 to 5 years after the ACS index event. During 2-5 years after the ACS index event, (1) the proportion of patients treated with 1 AP in NSTEMI subgroup was numerically lower than STEMI and UA subgroups; (2) the proportion of patients treated with 2+ AP in NSTEMI subgroup was numerically higher than STEMI and UA subgroups; (3) the proportion of patients treated with 2+ AP in invasive subgroup was numerically higher than non-invasive subgroup.

In the study, 227 patients (9.7%, 227/2,334) had 286 composite clinical events of all-cause mortality, MI and stroke (2+ AP subgroup numerically higher than 0 AP and 1 AP subgroups;

NSTEMI subgroup numerically higher than STEMI and UA subgroups; non-invasive subgroup numerically higher than invasive subgroup).

In the study, 65 patients (2.8%, 65/2,334) were recorded death, and the main reason leading to death was cardiovascular and cerebrovascular events. A total of 105 patients (4.5%, 105/2,334) had 120 MI events, 62.8% of which were NSTEMI and 97.5% led to hospitalization. A total of 88 patients (3.8%, 88/2,334) had 101 stroke events, 89.2% of which were ischemic stroke, and 90.1% led to hospitalization. A total of 214 patients (9.2%, 214/2,334) reported 290 bleeding events, 93.4% of which were minor bleeding and 53.4% led to outpatient visit.