OBSERVATIONAL STUDY REPORT SYNOPSIS

TIGRIS: Long-Term rIsk, clinical manaGement and healthcare Resource utilisation of stable coronary artery dISease in post myocardial infarction patients

Milestones:

Final protocol	3 April 2013
Start of data collection from patients	19 June 2013
Baseline interim results	16 June 2015
12-month interim results	30 August 2016
End of data collection from patients	31 March 2017 (27 March 2017 in Japan)
Statistical Analysis Plan finalised	6 July 2017
Database lock	26 July 2017
Final results Tables	26 February 2018
Final report	7 March 2018

Phase of development: Not Applicable – Observational study

Sponsor: AstraZeneca

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

Background/Rationale: The purpose of the TIGRIS study was to provide real-word data on the burden of both cardiovascular (CV) and bleeding events in a heterogenous population of high-risk patients 1-3 years post-myocardial infarction (MI) to assess outcomes during the years following a MI. This study complements the PEGASUS-TIMI 54 trial, which showed that dual antiplatelet therapy with ticagrelor 60mg BID and aspirin in high-risk post-MI patients 1-3 years from their index MI reduced the risk of cardiovascular death, myocardial infarction and stroke by 16% compared with aspirin monotherapy during a 3-year follow-up. It also adds to the evidence base from retrospective observational studies conducted using secondary healthcare data sources in individual countries. TIGRIS provides evidence from a global perspective. Being a prospectively conducted study, it was also able to collect patient-reported outcomes, including self-reported health status.

Objectives: The objectives were assessed in a real-world patient population with a history of MI 1-3 years ago and at high risk of developing atherothrombotic events at study entry. The primary objective was to describe prospectively and longitudinally during a 24-month follow-up period:

- Event rates and time to first occurrence of the composite of myocardial infarction, unstable angina with urgent re-vascularisation, stroke or death from any cause (primary composite)
- Healthcare resource utilisation (HRU) associated with cardiovascular events

Secondary objectives of the study were to describe during the 24-month follow-up period:

- The rate of ischaemic events and time to first occurrence of the composite of MI, unstable angina with urgent re-vascularisation, ischaemic stroke, CV death or death with unknown reason (secondary ischaemic composite)
- The rate of bleeding events requiring hospitalisation

[redacted]

Study design: TIGRIS was a multi-centre, observational, prospective longitudinal cohort study.

Data source: Data collection was performed at 334 study sites, in 25 countries from the following regions: Europe, North America and Australia, Latin America and Asia. Patients were recruited from cardiologists and from General Practitioners (GP)/family doctors. The majority of investigator sites were cardiology clinics. Information on the MI event, co-morbidities, clinical outcomes, treatment and HRU were collected during the initial visit. The patient was then contacted every 6-months subsequently for a follow-up for up to 24-months. Follow-up information was collected using two different methods depending on the country or study site: call-centre or non-call centre. Information was collected using an electronic case report form entered by an interviewer at a call centre (via a telephone call) or directly by a study nurse for non-call centres (face-to-face at a site visit, on the telephone or from medical notes). All events were confirmed by the study sites, after referral to the patient's medical notes. A total of 18 countries used interviewers at call centres and 8 countries used study nurses at medical sites (non-call centre model), with Spain having a mixture of both call centres (14 sites) and non-call centre sites (5 sites). Patients were enrolled 12 to 36 months after index MI with up to 24 months of follow-up, giving a post-MI study period of 1 to 5 years after the index MI.

Study population: The study population included 9,176 post-MI patients with a history of MI 12-36 months prior to enrolment into the study and with a defined high risk of developing atherothrombotic events. High risk was defined as having one or more of the following qualifying risk factors: age ≥ 65 years, diabetes mellitus requiring medication, multi-vessel coronary artery disease (CAD), chronic non-end stage renal dysfunction, history of MI prior to the index MI. Patients were followed for up to 24 months from enrolment (up to 36 months in some countries). The first patient was enrolled on 19 June 2013 and the last patient enrolled on 30 November 2014. The study was terminated in all countries by 31 March, 2017 (27 March 2017 in Japan), after a minimum of 24 months had passed since the enrolment interview (baseline) for each patient.

Inclusion Criteria: The patient population consisted of post-MI patients who gave informed consent, were aged 50 years or older with a documented history of presumed spontaneous MI, with their most recent MI occurring between 12-36 months prior to enrolment and having *at least* 1 of the qualifying risk factors.

Exclusion criteria: Patients were not eligible to participate in the study if any of the following exclusion criteria were present:

- 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 where interpreter services are not reliably available, psychiatric disturbances, alcohol or drug abuse)
- Presence of serious/severe co-morbidities which, in the opinion of the investigator, may limit life expectancy (<1 year)
- Current participation in a blinded randomized clinical trial
- Patients receiving treatment with ticagrelor at enrolment

Outcomes: The primary outcome was a composite of the first incidence of MI, unstable angina with urgent re-vascularisation, stroke (both ischaemic and haemorrhagic) and all cause death during the 24-month follow-up period confirmed by a physician. The secondary ischaemic outcome was a composite of the first incidence of MI, unstable angina with urgent revascularisation, ischaemic stroke, CV death or death with unknown reason, during the 24-month follow-up period confirmed by a physician. The secondary CV outcome was a composite of the first incidence of MI, stroke, CV death or death with unknown reason.

Incidence rates were used to assess the risk of a CV event after the index MI, calculated for each year after index MI starting at index MI plus one year. The person-time denominator was calculated for all the time-dependent analyses of rates for the full follow-up period available across all the countries (0-24months) with time in the study censored at 24-months calendar time from enrolment date.

HRU associated with CV and bleeding events requiring medical attention was assessed. All physician-confirmed hospitalisations for all CV and bleeding events in the 24-month follow-up period were included in analyses- with rate of hospitalisations described per 100 person-years. Patient-reported HRU other than hospitalisations (hospitalisations defined as a hospital stay of 24 hours or more) were also described- including GP/family doctor visits, cardiologist visits, other specialist visits and emergency room visits.

[redacted]

Statistical methods:

Descriptive statistics included the number of observations, mean, median, standard deviation, inter-quartile ranges (25^{th} and 75^{th} quartiles) for continuous variables and frequency and percentages for categorical variables and, where indicated, two-sided 95% confidence intervals were calculated to aid interpretation. The number and percentage of missing values were reported. Descriptive results were stratified by characteristics of the Index MI (time between index MI and baseline; 12-23 months, 24-36 months, MI type, clinical management), gender, region and qualifying risk factors.

[redacted]

For the incidence rates [redacted] the date of the first CV event of interest defined the end of the follow-up period. If no event occurred during the time interval of interest, then the end of patient follow-up time was the earliest of (1) the end of the time interval or (2) the date of last contact if this is before the end of the time interval or (3) date of death if it occurred before the end of the time interval.

Results:

Baseline characteristics of participants: For the primary and secondary objectives, 9,044 patients were included in analyses – excludes those patients (132) who either voluntarily discontinued (120) or were lost to follow up before the 6-month visit (12). With the exception of the antithrombotic treatment at baseline, baseline characteristics were similar in the subgroup of patients who entered the study after 1-2 years from index MI versus those who entered after 2-3 years from index MI,

The majority of the study population included in analyses were male (76.09%) while the mean age of patients was 66.9 years. The three most common qualifying risk factors (N=9,044) were multivessel CAD (65.9%) and being age ≥ 65 years (62.3%), followed by diabetes mellitus requiring medication (30.5%). This trend was seen throughout the 4 regions, although proportions varied. Europe had a higher proportion of the population aged 65 years or older (66.1%) in comparison to those with multi-vessel CAD (64.4%).

Differences in baseline characteristics were noted between regions. At baseline, patients in the Asian and South American regions were younger than the overall population. Asia also had the highest percentage prevalence of diabetes mellitus requiring medication (37.3%), despite a lower mean BMI (24.5kg/m^2). Differences were also observed between regions in the characteristics of the index MI; STEMI being the most common type of index MI in the regions of Asia (64.2%), Europe (51.2%) and Latin America (48.2%) respectively, while NSTEMI was the most frequent type observed in North America and Australia (57.1%).

Cardiovascular and bleeding event rates: Overall, there were in total 1,207 physician confirmed CV events in the 24-month follow-up. Of these, 59 were not given a final discharge diagnosis. The majority of CV events were coronary events constituting 61.5% of all CV events for the total population. In the total population, the incidence rate for the primary composite (MI, unstable angina with urgent re-vascularisation, stroke or death from any cause) for the first event was 3.6 per 100 person-years (95% confidence interval (CI) 3.33-3.90). For the secondary ischaemic composite (MI, unstable angina with urgent re-vascularisation, ischaemic stroke, CV death or death with unknown reason), the incidence rate was 2.9 per 100 person-years (95% confidence interval 2.7-3.2). For the secondary CV composite (MI, stroke, CV death or death with unknown reason) the incidence rate was 2.4 per 100 person-years (2.2-2.7). Overall, there was a relatively consistent incidence rate from time since the index MI for the composite outcomes. In total, 109 patients had any bleeding event requiring medical attention, the incidence rate in the total population was 0.6 per 100 person-years (0.5-0.7), with constant rates across time since index MI.

Physician-reported hospitalisations for CV events: During the 24-month follow-up, there were 1,207 physician-confirmed hospitalisations related to all cardiovascular events in the patients who provided follow-up data (N=9,044). Of these, 198 of the hospitalisations included at least a 24-hour stay in an intensive care unit (16.4% of total hospitalisations). Overall, 89.8% of patients in the total population did not report a hospitalisation due to cardiovascular events during the time-period, while 0.6% were hospitalised 3 or more times.

The rate of hospitalisations (per 100 person-years) related to cardiovascular events (95% confidence interval) during the 24-month follow-up was 6.9 (6.5-7.3) for any hospitalisation, and 1.1 (1.0-1.3) for intensive care unit hospitalisations. For any hospitalisation related to cardiovascular events, the mean (median) length of stay was 8.9 (5.0) days and was similar for each stratification according to time since index MI.

The rate of hospitalisations was substantially higher for those patients with diabetes requiring medication (9.3 (8.5-10.2)), chronic non-end stage renal dysfunction (12.5 (10.7-14.6)) or second prior MI (12.8 (11.2-14.6)) . The length of stay was longer for those patients with chronic non-end stage renal dysfunction (mean 14.2 days, median 7 days) or second prior MI (mean 11.7 days, median 7 days)

[redacted]

[redacted]

Conclusion: The burden of recurrent CV events in this high-risk post-MI patient population remained elevated during the follow-up. Furthermore, the cumulative risk of a recurrent CV event in these patients increased linearly from 1 year up to 5 years post-MI. The hazard was higher for patients with certain comorbidities, in particular with each of the individual qualifying risk factors and those with a history of PAD compared to those with no history of PAD. The event rate for bleeding requiring hospitalisation for at least 24-hours or that occurred during a hospitalisation was low. This study, together with evidence from other real-world observational studies indicates, that long-term secondary prevention programmes are warranted in this high-risk population to reduce the risk of recurrent CV events, but must be balanced, as always, with increased risk of side-effects.

Publications:

- *Westermann D ,Goodman SG, et al. Rationale and design of the long-Term rIsk, clinical manaGement, and healthcare Resource utilisation of stable coronary artery dISease in post-myocardial infarction patients (TIGRIS) study. Clinical Cardiology 2017:40:1197-1204.*
- *Goodman SG, Nicolau JC, et al. Longer-term oral antiplatelet use in stable post-myocardial infarction patients: Insights from the long Term rIsk, clinical manaGement and healthcare Resource utilisation of stable coronary artery dISease (TIGRIS) observational study. International Journal of Cardiology 2017:236:54-60.*