CSR Synopsis

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ALETHEIA

An observational, register-based study on ticagrelor 60 mg treatment patterns and event rates in clinical practice in the US and Europe

Clinicaltrials.gov registration: **NCT04568083**

Milestones:

Milestone	Date
Study design concept approved	Mar 2019
Kick-off meeting with external scientific advisory committee	Jul 2019
Study protocol (v1.0) approved	Jun 2019
Study protocol amendment (v2.0) approved	Feb 2020
Master statistical analysis plan finalized	Nov 2020
Study protocol amendment (v3.0) approved	Mar 2021
Data access completed for all countries/data sources	Jun 2021
Data analyses finalized (meta-analyses of data source-level results)	Dec 2021
Study report approved	Dec 2021

Sponsor: AstraZeneca

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Background/rationale: Patients with a history of myocardial infarction (MI) are at increased risk of cardiovascular events. The PEGASUS-TIMI 54 trial, completed in 2015, demonstrated that treatment with ticagrelor 60 mg, combined with low-dose acetylsalicylic acid/aspirin (ASA), reduced major adverse cardiovascular events in patients with a prior MI (one to three years prior) and additional atherothrombotic risk factors, compared to ASA alone. Clinical guidelines now recommend the extension of dual antiplatelet therapy (DAPT) beyond 12 months in patients with a history of MI who have tolerated 12 months of DAPT without bleeding complications. However, data from routine clinical practice are scarce on patient characteristics, treatment persistence, bleeding and cardiovascular (CV) outcomes of ticagrelor 60 mg in patients with a prior MI.

Objectives: The primary objective of this study was to describe the patient characteristics, persistence to treatment, and bleeding requiring hospitalization in patients initiating treatment with ticagrelor 60 mg after an MI in real-world clinical practice.

The secondary objectives were to describe the risk of the composite of MI, stroke and all-cause mortality, as well as treatment persistence, and risk of bleeding and CV outcomes in patient subgroups.

Exploratory objectives included analyzing the associations between baseline patient characteristics and the risks of bleeding and CV outcomes, respectively. An additional exploratory objective was to describe the risk of the individual components of bleeding and CV outcomes. For contextualization, characteristics of patients treated with a $P2Y_{12}$ inhibitor other than ticagrelor (clopidogrel, prasugrel, or ticlopidine) and those not treated with any $P2Y_{12}$ inhibitor (clopidogrel, prasugrel, ticlopidine, or ticagrelor) at a comparable timepoint to the ticagrelor patients after their first MI during the eligibility period were also described.

Study design: Observational cohort study

Data source: Health register and claims data from the United States (US; Optum Clinformatics, IBM MarketScan, and Medicare) and Europe (Sweden, Italy, the United Kingdom [UK], Germany)

Study population: The primary population included patients initiating ticagrelor 60 mg (index date) ≥12 months after their MI (qualifying MI), meeting eligibility criteria broadly aligned with the PEGASUS-TIMI 54 trial and the US label.

Inclusion criteria: A first prescription of ticagrelor 60 mg ≥12 months (12-month cohort) after their most recent hospitalization with a primary diagnosis of MI (i.e., their qualifying MI)

Exclusion criteria: A history of ischemic stroke, intracranial bleeding, hepatic impairment, gastrointestinal bleeding, stage 5 chronic kidney disease, or renal failure, or concomitant use of an anticoagulant or a strong CYP3A4 inhibitor or inducer

Statistical methods: Patient characteristics and treatment persistence were summarized using descriptive statistics. Cumulative incidence of events at pre-specified timepoints were calculated using the Kaplan-Meier method. Incidence rates of outcome events per 100 person-years were calculated as the total number of patients with the event during follow-up divided by the total person-time at risk. All-event rates were also estimated, in which patients were not censored at the occurrence of the outcome of interest. The primary analyses were based on an on-treatment approach, and intention-to-treat were performed as sensitivity analyses. Cox proportional hazards regression models were used to investigate patient characteristics associated with an increased risk of bleeding requiring hospitalization and of the CV composite. The sample size weighting method was used to pool patient characteristics across data sources. Meta-analyses were applied to generate pooled outcome estimates, if deemed appropriate after assessment of feasibility and data-source level variations in data coverage

and results, complemented with sensitivity analyses. Unless specifically stated otherwise, the results presented refer to the pooled estimates.

Results: After applying inclusion and exclusion criteria, the final primary population included 7,035 patients. Most patients were male (71%), and the median age was 67 years. The median time between MI and the index date (initiation of ticagrelor 60 mg) was 15.2 months. The vast majority of patients (95%) had received prior treatment with ticagrelor 90 mg between the qualifying MI and index date.

Treatment persistence of ticagrelor 60 mg varied between data sources, and ranged from 61.0% to 83.2% at 12 months and from 31.4% to 71.1% at 24 months. Within the first 6 months, the percentage of patients with an adherence level of ≥80% ranged from 79.9% to 88.6%.

The 7,035 patients in the primary population across all seven data sources contributed with a total of 6573 PYs on treatment. The *a priori* threshold of 5,000 PYs on treatment was therefore exceeded, and clinical outcomes were analysed.

The incidence rates of bleeding requiring hospitalization was 0.96 [95% CI: 0.70–1.33] per 100 PYs within 0-12 months and 0.81 [0.60–1.08] within 0-24 months when all data sources were included. Heterogeneity was observed (0-12-months: I^2 58.9%; 0-24-months: I^2 39.7%). When the two smallest data sources (from the UK and Germany) were excluded, heterogeneity was diminished (I^2 0% for 0-12 and 0-24 months), and the incidence rate was 0.72 [0.49–1.06] within 0-12 months and 0.67 [0.48–0.94] within 0-24 months. The cumulative incidence of bleeding requiring hospitalization was 0.96% [95% CI: 0.69–1.33] at 12 months and 1.52% [95% CI: 1.09–2.12] at 24 months. Heterogeneity was observed at 12 months (I^2 59.8%), and to some extent at 24 months (I^2 7.6%). When the two smallest data sources were excluded, heterogeneity decreased (I^2 12.3% at 12 months and 0% at 24 months), and the cumulative incidence was 0.71 [0.48–1.04] at 12 months and 1.33 [0.9–1.97] at 24 months.

The incidence rates of the secondary CV composite was 3.33 [95 CI: 2.76–4.02] per 100 PYs within 0-12 months and 3.46 [2.95–4.07] within 0-24 months when all data sources (except US Optum and US MarketScan, which did not capture data on death) were included. There was no heterogeneity (I^2) within 0 to 12 months, while heterogeneity was observed within 0 to 24 months (60.2%). After exclusion of the two smallest data sources, heterogeneity (I^2) within 0 to 24 months decreased to 34.1% and the incidence rate was 3.15 [2.57–3.84] within 0 to 12 months and 3.21 [2.70–3.81] within 0 to 24 months. The cumulative incidence of the secondary CV composite was 3.33 (95 CI: 2.75–4.04) at 12 months and 6.72 (95 CI: 5.62–8.02) at 24 months. There was no heterogeneity at 12 months, but heterogeneity was observed at 24 months (I^2 81.3). When the two smallest data sources were excluded, heterogeneity remained similar (I^2 0% at 12 months, 82.8% at 24 months) and the cumulative incidence was 3.14% (2.56–3.85) at 12 months and 6.16% (5.09–7.47) at 24 months.

Conclusion: Patients initiating ticagrelor 60 mg at least one year after their MI in routine clinical practice had a median age of 67 years and 71% were males. Overall, 16% had CKD, 33% had diabetes, and 12% had a history of more than one prior MI. Treatment persistence at 12 months ranged from 61% to 83%. At 12 months, the cumulative incidence (95% CI) of bleeding requiring hospitalization was 0.96% (0.69–1.33). The 12-month cumulative incidence of the composite CV outcome (MI, stroke and all-cause mortality) was 3.33% (2.75–4.04). Post-MI patients treated with ticagrelor 60 mg in contemporary clinical practice in the US and Europe, in alignment with clinical trial evidence and current guideline recommendations, thus have a 3.5-fold higher risk of death or hospitalization for MI or stroke compared to the risk of bleeding requiring hospitalization.