Adv Ther (2019) 36:1595–1605
https://doi.org/10.1007/s12325-019-00972-z

ORIGINAL RESEARCH

YINGLONG: A Multicenter, Prospective, Non-Interventional Study Evaluating the Safety and Tolerability of Ticagrelor in Chinese Patients with Acute Coronary Syndrome

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Received: January 21, 2019 / Published online: May 22, 2019

ABSTRACT

Introduction: Ticagrelor is an oral, reversible, direct-acting $P2Y_{12}$ receptor inhibitor approved for the prevention of cardiovascular events in acute coronary syndrome (ACS). In China, drug intensive monitoring regulations for new drugs require additional safety data post-approval.

Methods: YINGLONG, a single-arm, phase-IV, 1-year, non-interventional study, described the safety of ticagrelor 90 mg twice daily in Chinese patients (≥18 years) with ACS treated with ≥1 dose of ticagrelor. Primary outcomes were the incidence of adverse events (AEs), in particular, PLATelet inhibition and patient Outcomes (PLATO)-defined bleeding AEs, and other serious AEs during the 1-year follow-up. Key secondary outcomes were the incidence of major cardiovascular events.

Results: Patients (n=1041, median age 61.0 years) had started ticagrelor and had post-dose data. Median duration of ticagrelor

A full list of the YINGLONG study investigators can be found in Supplementary File 4.

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12325-019-00972-z) contains supplementary material, which is available to authorized users.

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treatment was 357 days; 577 patients (55.4%) completed 1-year ticagrelor treatment; 973 patients (93.5%) completed 1-year follow-up. Overall, 38.7% of patients reported an AE during treatment. The most common AEs were dyspnea (n=37, 3.6%), petechiae (n=30, 2.9%), and chest discomfort (n=28, 2.7%). Serious AEs, excluding bleeding, were reported in 9.8% of patients during treatment. Incidence of PLATO-defined major bleeding events was 1.1% (n=11). Of the 21 deaths that occurred during the study (8 post-treatment), 1 was a fatal bleed. Major cardiovascular events were reported in 37 patients (3.6%).

Conclusions: Ticagrelor was well tolerated with a low rate of PLATO-defined major bleeding events in Chinese ACS patients. Safety results were consistent with the known ticagrelor profile.

Trial Registration: ClinicalTrials.gov identifier, NCT02430493.

Funding: AstraZeneca Investment (China) Co., Ltd.

Keywords: Acute coronary syndrome; Bleeding; Cardiology; Chinese patients; Safety; Ticagrelor

INTRODUCTION

In China, an estimated 290 million people have cardiovascular (CV) disease [1]. Acute coronary syndrome [ACS; which includes unstable angina (UA), non–ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI)] has high morbidity, mortality, and economic burden [2, 3]. In China, the reported mortality rate of patients hospitalized with ACS is 5% [4], with poorer post-discharge outcomes for patients with NSTEMI compared to those with STEMI [5]. Improved adherence to ACS guidelines may help enhance patient outcomes in China [6].

Ticagrelor is an oral, direct- and rapid-acting reversible $P2Y_{12}$ receptor antagonist [7], approved for use in patients with ACS in the United States [8] and many other countries. Ticagrelor inhibits platelet aggregation by antagonizing the binding of adenosine diphosphate at the $P2Y_{12}$ receptor [9, 10]. Ticagrelor has an additional adenosine-mediated mechanism of action via therapeutically relevant inhibition of equilibrative nucleoside transporter 1 (ENT-1) to inhibit cellular adenosine uptake [11]. In China, co-administration of ticagrelor with aspirin (ASA) is indicated to reduce the rate of CV death, myocardial infarction (MI), and stroke in patients with ACS or a history of MI and with at least 1 high-risk factor of developing an atherothrombotic event [12]. European and Chinese guidelines recommend ticagrelor as first-line treatment for patients with ACS [13–15].

The global PLATelet inhibition and patient Outcomes (PLATO) trial, which included a broad spectrum of 18,624 patients with ACS, showed ticagrelor to be superior to clopidogrel in reducing fatal and non-fatal CV events, without an increase in the rate of overall major bleeding [16]. Efficacy and safety results in the Asian subgroup were consistent with those of the overall population [17]; however, only a minority (n =587, 3.1%) of patients in the PLATO trial were Chinese, 416 of whom were randomized in mainland China (AstraZeneca data on file). Ticagrelor was approved in 2012 by the China Food and Drug Administration (CFDA). However, based on CFDA drug intensive monitoring (DIM) regulations that came into force in 2011, further phase IV safety data on ticagrelor were required for patients with ACS in China. In accordance with this mandate, and to obtain a real-world assessment of the safety profile and CV event rates in a large ethnically Chinese population, 2 phase IV studies (DAYU and YINGLONG), comprising approximately 3000 Chinese patients with ACS, were conducted. The interventional DAYU study comprised 2004 Chinese patients with ACS [18].

The present post-authorization, non-interventional YINGLONG study assessed the safety and tolerability of ticagrelor treatment over 1 year in Chinese patients with ACS.

METHODS

Study Design

The YINGLONG study (NCT02430493) was a non-interventional, single-arm, prospective

cohort, open-label, multicenter, phase IV trial conducted in the cardiology departments of tier 3 hospitals in China. Data were collected corresponding to routine clinical practice, ticagrelor was prescribed according to the investigator's decision, and ticagrelor tablets were not supplied by the study sponsor. Patients who discontinued ticagrelor treatment before 12 months were encouraged to continue the study visits according to the protocol until the end of the study. The feasibility and quality of the site were assessed using a feasibility questionnaire prior to site confirmation. Investigators (cardiologists) were selected nationally on the basis of experience and ability to manage a reasonable number of patients, and were trained prior to study initiation on standardized definitions of study terms [e.g., ACS diagnoses, inclusion/exclusion criteria, safety events, and the process of investigating adverse events (AEs)]. Investigators were responsible for the classification of bleeding and CV events according to protocol definitions. Major CV events and AEs were documented from enrollment to the last visit. All eligible patients were consecutively enrolled as quickly as possible after presentation on the first day of hospitalization following the index ACS event, until the required number of patients were attained. The follow-up period started from when informed consent was provided at the index ACS hospital admission.

The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation/Good Clinical Practice Guidelines and followed applicable regulatory requirements, including AstraZeneca's policy on bioethics. The local Institutional Review Boards or Independent Ethics Committees approved the final protocol and amendment.

Objectives

The primary objectives of the YINGLONG study were to describe the safety and tolerability of ticagrelor during a 1-year follow-up of Chinese patients with ACS treated with ticagrelor. Primary objectives were assessed by AEs (characteristics, reporting rate, severity, and causality), especially the bleeding events, and other serious adverse events (SAEs). The incidence of major CV events (including CV death, non-fatal MI, or stroke) during the 1-year follow-up was a secondary objective of the study.

Patients

Eligible patients were ethnic Chinese men or women aged $\geq$18 years with an index event of non–ST or ST-segment elevation ACS who had been initiated on ticagrelor treatment. Qualifying events for inclusion were hospitalization for chest pain and potential ACS with documented cardiac ischemic symptoms of $\geq$10 min at rest and either (1) persistent ST-segment elevation $\geq$ 1 mm (0.1 mV) in $\geq$2 contiguous leads and primary percutaneous coronary intervention (PCI) planned, (2) new or presumed new left bundle-branch block and primary PCI planned, or (3) cardiac ischemic symptoms of $\geq$10 min at rest and at least ST-segment changes on electrocardiogram (ECG) indicative of ischemia and/or positive biomarker evidence of myocardial necrosis. Patients were excluded if they had participated in another clinical study of an investigational product in the past 6 months, had been previously enrolled in the present study, or had an allergy to or any other contraindications to ticagrelor as indicated in the Chinese prescribing information [12]. Written informed consent was obtained from all patients.

Safety Assessments

After study inclusion, clinic visits were scheduled at 1, 3, 6, and 12 months (each $\pm$7 days) for safety assessments and for reporting of concomitant medications. AEs were also collected from routine medical records. All AEs were coded using version 19.1 of the Medical Dictionary for Regulatory Activities (MedDRA). Bleeding AEs were classified by the local investigator according to PLATO definitions (Supplementary File 1). CV events (CV death, MI, and stroke) were also reported as AEs.

Sample Size Calculation and Statistical Analyses

Given that the Chinese DIM regulations for new drugs require post-authorization safety data on at least 3000 patients, and considering that the DAYU study planned to enroll 2000 patients, approximately 1000 patients with ACS would need to be enrolled in the YINGLONG study. The safety population included all patients who received at least 1 dose of ticagrelor and for whom any post-dose data were available. All analyses were performed on the safety population unless otherwise stated. Statistical analyses were performed using SAS v.9.4 (SAS Institute Inc., Cary, NC, USA). Descriptive statistics were used to summarize safety data for the safety population in terms of frequency and percentage of patients in each category for the bleeding events, AEs, SAEs, etc. Kaplan–Meier (K-M) estimates of the cumulative risk to the first occurrence of bleeding events, or any event for major CV events, were calculated and provided. The data management and statistical analyses were performed by the sponsor.

RESULTS

Patients and Treatment

A total of 1066 patients with ACS from across 19 investigational centers in 10 provinces or municipalities of China (participating sites included in Supplementary File 2) were enrolled; the first patient was enrolled on May 28, 2015, and the last patient completed the study on March 29, 2017. Figure 1 shows the patient disposition. Of all the patients included in the study, 577 (55.4%) patients continued ticagrelor for at least 1 year and 973 (93.5%) patients completed the 1-year follow-up. Table 1 shows the demographic and baseline characteristics of the safety population. A total of 1041 patients were included in the safety population. The most common reason for premature termination of ticagrelor was economic burden (13%); 1.4% of patients discontinued because of bleeding events (Fig. 1). Overall, 68 (6.5%) patients discontinued the study, with the most common reasons being loss to follow-up (n =28, 2.7%) and death (n=21, 2.0%). The median age was 61.0 years, with 89.7% of patients being < 75 years old. The index event was STEMI in 63.5% of patients, NSTEMI in 24.5%, and UA in 12%. Overall, 1007 (96.7%) patients had at least 1 concomitant medication, out of which 61.6% were reported to have received ASA. The mean [standard deviation (SD)] duration of ticagrelor treatment was 246 (146) days; the median exposure was 357 days. Overall, 64.8% and 47.1% of patients had > 6 months and > 2 months of exposure, respectively, but only 0.5% were treated for> 13 months and <14 months.

Adverse Events

During treatment, 38.7% of patients in the safety population reported at least 1 AE (including bleeding and CV events); 13.5% of the AEs were deemed by the investigator to be causally related to ticagrelor, with 3.9% leading to ticagrelor discontinuation. During treatment, most patients (26.1% and 7.9%) reported AEs that were considered by the investigator to be mild or moderate in intensity, respectively. A total of 117 (11.2%) of patients reported at least 1 SAE during treatment; these events were mild in 1.8%, moderate in 5.1%, and severe in 4.3% of patients. Overall (i.e., during treatment and post-treatment), dyspnea, UA, and chest discomfort were the most common AEs reported by 3.6, 3.3, and 3.0% of patients, respectively. The most common AEs during ticagrelor treatment were dyspnea (n=37, 3.6%), petechiae (n= 30, 2.9%), and chest discomfort (n=28, 2.7%). The most common AEs leading to ticagrelor discontinuation included dyspnea (n=5, 0.5%), gastrointestinal (GI) hemorrhage (n=4, 0.4%), coronary artery disease (n=3, 0.3%), and rash (n =3, 0.3%).

Supplementary File 3 shows AEs that occurred in ≥1% of patients by causality assessment. Overall, independent of the causality assessment and excluding major CV and bleeding events, 383 (36.8%) patients experienced at least 1 AE, most of which were mild in intensity (68.7%). A total of 21 (2.0%) patients

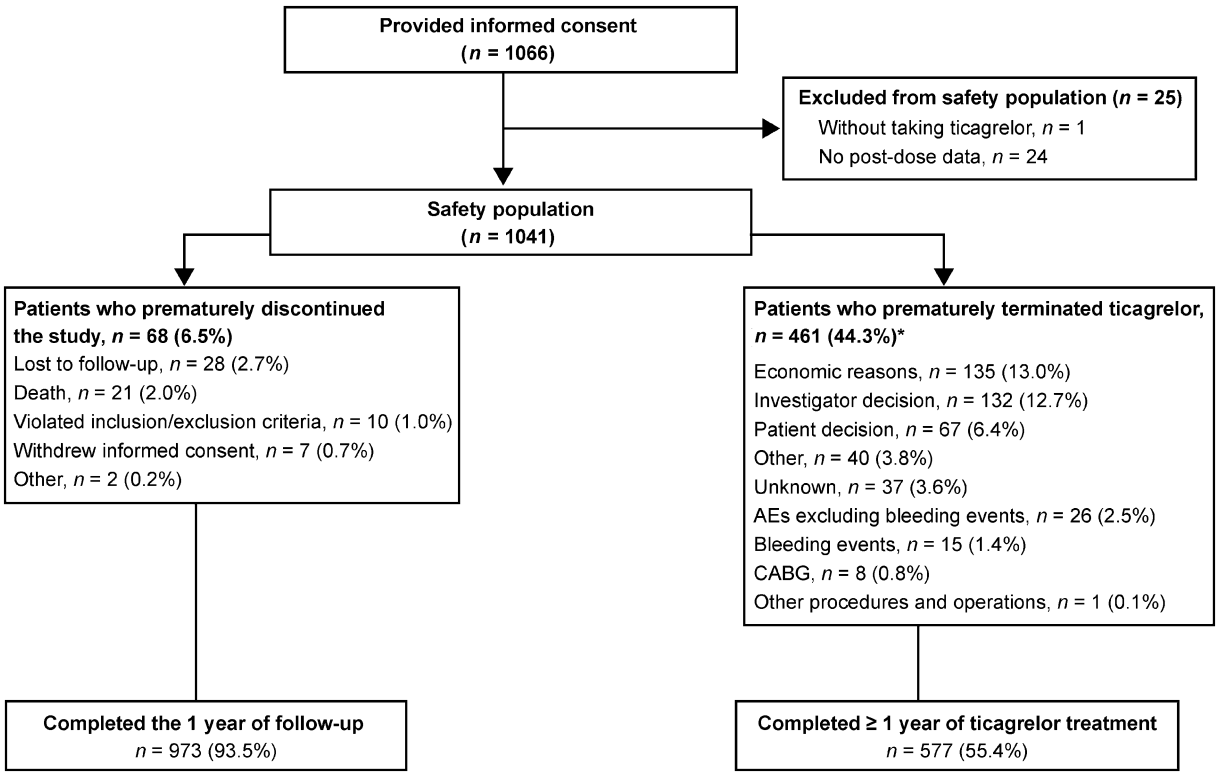

Fig. 1 Patient disposition. *Three patients who discontinued ticagrelor before providing informed consent are excluded. *AE* adverse event, *CABG* coronary artery bypass grafting

discontinued ticagrelor because of a non-bleeding/non-major CV event; 69 (6.6%) of the AEs were judged by the investigator to be causally related to ticagrelor.

During treatment, a total of 102 (9.8%) patients reported at least 1 SAE, excluding bleeding events. SAEs that led to ticagrelor discontinuation were reported by 0.7% of patients, and SAEs causally related to ticagrelor were reported by 0.4% of patients. The 3 most commonly reported SAEs (excluding bleeding) during treatment by preferred term were UA (*n*=23, 2.2%), coronary artery disease (*n*=13, 1.2%), and acute MI (*n*=9, 0.9%). The most common SAEs by preferred term resulting in ticagrelor discontinuation were GI hemorrhage (*n*=4, 0.4%), coronary artery disease (*n*=3, 0.3%), cardiac failure (*n*=2, 0.2%), and upper GI hemorrhage (*n*=2, 0.2%). The most common SAE by preferred term deemed causally related to ticagrelor treatment was GI hemorrhage (*n*=7 patients, 0.7%). Overall, there were 21 (2.0%) deaths, with 13 (1.2%) occurring during treatment and 8 (0.8%) during the post-treatment period. Two-thirds of all the deaths were CV deaths (*n*=14, 1.3%); 1 death (cerebral hemorrhage) was considered related to ticagrelor. The causes of CV deaths during the study were reported as acute MI, sudden cardiac death, heart failure, CV disease, cerebral hemorrhage, cerebral infarction, and unknown (5 patients).

Bleeding Events

Overall, 112 (10.8%) patients experienced at least 1 bleeding AE, and 107 (10.3%) reported bleeding AEs during treatment. During treatment, most bleeding AEs were mild (*n*=83, 8.0%), with fewer moderate (*n*=15, 1.4%) or severe (*n*=9, 0.9%) episodes. Sixteen (1.5%) patients experienced at least 1 bleeding SAE during treatment; this was classed as mild in 3 (0.3%), moderate in 5 (0.5%), and severe in 8 (0.8%) patients. Bleeding AEs that led to

Table 1 Patient demographics and baseline characteristics (safety population)

Characteristic	Number (%) of patients ($n=1041$)
Age, years, mean (range)	59.9 (25–89)
Age group	
< 75 years	934 (89.7)
≥ 75 years	107 (10.3)
Sex	
Male	822 (79.0)
Female	219 (21.0)
BMI, kg/m^2, mean (SD)	24.7 (3.2)
Ethnic group	
Han	1029 (98.8)
Other	12 (1.2)
Medical history	
MI	902 (86.6)
Hypertension	621 (59.7)
Coronary artery disease	536 (51.5)
Diabetes mellitus	266 (25.6)
Final diagnosis of index event	
Unstable angina pectoris	125 (12.0)
ST-segment elevation MI	661 (63.5)
Non-ST-segment elevation MI	255 (24.5)
Concomitant medications	
Proton-pump inhibitors	662 (63.6)
Antithrombotic agents	642 (61.7)
HMG CoA reductase inhibitors	640 (61.5)
Aspirin	620 (59.6)
Selective beta-blocking agents	534 (51.3)
Other cardiac preparations	456 (43.8)
Angiotensin-converting enzyme inhibitors	328 (31.5)
Use of GPIIb/IIIa inhibitors prior to first ticagrelor dose	4 (0.4)
Treatment approach at enrollment	
Invasive therapy[a]	836 (80.3)
Medically managed therapy	205 (19.7)

BMI body mass index, *CABG* coronary artery bypass grafting, *HMG CoA* 3-hydroxy-3-methylglutaryl-coenzyme A, *GP* glycoprotein, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *SD* standard deviation

[a] Invasive therapy means PCI or CABG during the index hospitalization; 91.5% of patients were planned for primary PCI

ticagrelor discontinuation occurred in 15 (1.4%) patients. These included GI hemorrhage (including upper GI hemorrhage; $n=6$), duodenal ulcer bleeding ($n=1$), gingival bleeding ($n=1$), epistaxis ($n=2$), hemoptysis ($n=1$), extradural hematoma after trauma ($n=1$), petechiae ($n=1$), subcutaneous hemorrhage ($n=1$), and cerebral hemorrhage ($n=1$). Bleeding AEs deemed by the investigator to be causally related to ticagrelor occurred in 89 (8.5%) patients. Table 2 shows the bleeding AEs (overall incidence ≥ 0.2%) by causality in the safety population. During treatment, 1 patient died from a bleeding SAE (cerebral hemorrhage) and another patient suffered a life-threatening intracerebral hemorrhage (ICH), both of which were spontaneous. Bleeding SAEs that led to ticagrelor discontinuation were experienced by 0.9% of patients, and bleeding SAEs deemed by the investigator to be causally related to ticagrelor were reported in 1.3% of patients.

Bleeding Events Classified According to PLATO Definitions

During treatment and post-treatment, 36 (3.5%) patients reported major and minor bleeding events within 12 months after the first exposure to ticagrelor, with a K-M estimated event rate [95% confidence interval (CI)] of 4.7% (3.3–6.5%). Most major and minor bleeding events

Table 2 Bleeding AEs (overall incidence ≥ 0.2%) by causality[a] and preferred term (safety population)

Preferred term	Ticagrelor 90 mg bid (n = 1041)		
	Related to ticagrelor n (%)	Not related to ticagrelor n (%)	Overall n (%)
Patients with at least 1 bleeding AE	89 (8.5)	23 (2.2)	112 (10.8)
Petechiae	28 (2.7)	3 (0.3)	31 (3.0)
Gingival bleeding	24 (2.3)	4 (0.4)	28 (2.7)
Epistaxis	16 (1.5)	6 (0.6)	22 (2.1)
Gastrointestinal hemorrhage	9 (0.9)	2 (0.2)	11 (1.1)
Subcutaneous hemorrhage	5 (0.5)	1 (0.1)	6 (0.6)
Hemoptysis	4 (0.4)	1 (0.1)	5 (0.5)
Occult blood positive	4 (0.4)	1 (0.1)	5 (0.5)
Upper gastrointestinal hemorrhage	4 (0.4)	0	4 (0.4)
Hematuria	2 (0.2)	1 (0.1)	3 (0.3)
Cerebral hemorrhage	1 (0.1)	1 (0.1)	2 (0.2)
Hematochezia	2 (0.2)	0	2 (0.2)
Occult blood	1 (0.1)	1 (0.1)	2 (0.2)
Skin hemorrhage	2 (0.2)	0	2 (0.2)

[a] Causality assessment was performed by the investigator. Entries show numbers of patients, not events. The table includes events regardless of whether the onset was during or after treatment with ticagrelor. AEs were coded using version 19.1 of the Medical Dictionary for Regulatory Activities (MedDRA)

AE adverse event, *bid* twice daily

were spontaneous bleeding events [34 (3.3%) patients], with 1 (0.1%) patient each reporting traumatic bleeding and procedural bleeding. The majority of the major and minor bleeding events occurred within the first 6 months of follow-up during the study. Overall, the composite of the major, minor, and minimal bleeding events occurred in 112 (10.8%) patients, the majority of whom (n=76, 7.3%) reported minimal bleeding only. Minor bleeding events occurred in 25 (2.4%) patients. Eleven (1.1%) patients experienced major bleeding events, of which fatal/life-threatening bleeding had an incidence of 0.6% (6 patients). There was 1 fatal bleed (see "Bleeding events").

Major Cardiovascular Events

Major CV events (composite of CV death/MI/stroke) were reported in 37 (3.6%) patients (49 events) during the 1-year follow-up; the K-M estimate of the 12-month event rate (95% CI) was 3.7% (2.7–5.1%). Figure 2 shows the K-M plot of time to first major CV event during the study. CV deaths were reported in 14 (1.3%) patients. Overall, 22 (2.1%) patients reported MI (27 events), half of whom had STEMI and the other half NSTEMI, with a K-M estimate of the 12-month MI event rate (95% CI) of 2.3% (1.5–3.4%). Eight (0.8%) patients had stroke (8 events; ischemic stroke in 6 patients, hemorrhagic stroke in 1 patient, and an undefined stroke type in 1 patient); the K-M estimate of the 12-month event rate (95% CI) was 0.8% (0.4–1.6%).

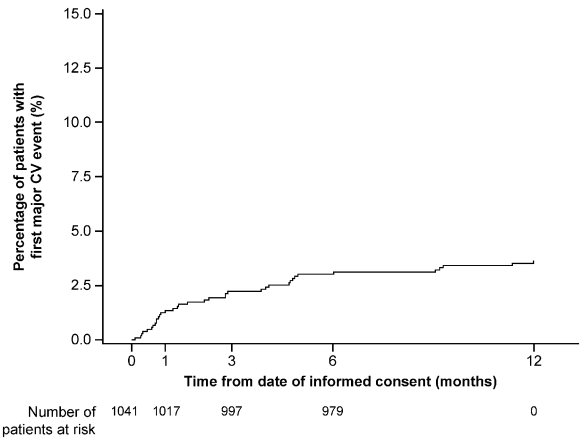

Fig. 2 Kaplan–Meier plot of time to first major cardiovascular event during the study. *CV* cardiovascular

DISCUSSION

YINGLONG was a 1-year, non-interventional study of ticagrelor treatment in Chinese patients with ACS, meant to reflect actual clinical practice, and of a population consistent with the Chinese prescribing information for ticagrelor. The YINGLONG study demonstrated that, under real-world conditions, 90 mg of ticagrelor twice daily for up to 1 year is associated with a low incidence of major bleeding events, major CV events, and SAEs in Chinese patients with ACS. Concomitant use of ASA was reported in approximately 60% of patients, which was lower than expected. For example, data from the nationwide Clinical Pathways for Acute Coronary Syndromes in China (CPACS) study described ASA being used in>90% of Chinese patients with ACS after discharge [4] and in 87% even after 12 months [19]. The low percentage of concomitant ASA use might be because of the investigators' concern about bleeding, or low-risk patients being diagnosed with ACS, and may have contributed to the lower than expected rate of bleeding side effects. Under-reporting of prior and concomitant medications, such as ASA and statins, in this observational study also cannot be ruled out. The incidence of PLATO-defined major bleeding events was 1.1%, of which fatal/life-threatening bleeding had an incidence of 0.6%; SAEs excluding bleeding were reported in 9.8% of patients during treatment. The majority of the bleeding was minimal (n=76, 7.3%), followed by minor (n=25, 2.4%). Most of the bleeding events occurred within the first 6 months of the treatment. The cumulative incidence of the composite of CV death/MI/stroke was 3.6%. One death (cerebral hemorrhage) judged by the investigators to be related to ticagrelor use was reported.

Some of these results are comparable to other ticagrelor studies in patients with ACS, such as the DAYU [18], PLATO [16], and retrospective Asian subgroup analysis of PLATO [17] studies, although there are some important differences. The DAYU study [18] was also a phase IV study of ticagrelor use in Chinese patients with ACS. However, in addition to DAYU involving more patients, there were some important differences between these studies, both in design and outcomes. In the interventional DAYU and PLATO studies, the initiation of ticagrelor was part of the study protocol and the drug was provided to patients during the study, while in the non-interventional YINGLONG study, the decision to initiate ticagrelor was based on clinical practice independently from study participation and the product was not supplied by the sponsor. This can better reflect actual clinical practice and minimize potential impacts (whether positive or negative) on treatment compliance. Other differences between YINGLONG and DAYU were that YINGLONG had no collection of laboratory safety data included in the protocol and CV events were also reported as AEs, whereas the DAYU protocol included collection of safety samples and CV events were reported separately from AEs. Not including any protocol-mandated laboratory sampling in YINGLONG reduced the intervention of local clinical routines to a minimum.

Both Chinese ticagrelor phase IV studies—DAYU and YINGLONG—showed similar safety results and incidences of CV events. In DAYU, during the 1-year follow-up treatment with ticagrelor, the incidences of fatal/life-threatening and PLATO-defined major bleeding events were 0.8% and 1.3%, respectively; the incidence of the composite of CV death/MI/stroke was 4.2%, and SAEs other than bleeding were reported in 5.8% of the patients during treatment [18]. These rates were comparable with those found in YINGLONG.

However, there are important differences in the rates of major bleeding and dyspnea between PLATO [16] and YINGLONG that deserve mention. Such differences should be interpreted with respect to the different study designs, PLATO being a randomized, controlled, phase III trial and YINGLONG being a non-interventional, phase IV study. The higher rate of major bleeding reported in PLATO (11.6%) compared with YINGLONG (1.1%) could be accounted for by several reasons. For example, the PLATO trial required patients to not only have ACS but also additional risk factors, which may have impacted the bleeding risk. Patients planned for urgent coronary artery bypass

grafting (CABG) are less likely to be put on ticagrelor because of label restrictions, and hence were not eligible for YINGLONG, whereas in the PLATO trial such patients were allowed. A large part of the major bleeds in the PLATO trial were procedure- and CABG-related [16]. There were more patients on heparin/low–molecular weight heparin in PLATO [16] (51.6%) than in YINGLONG (where 23.5% and 10.0% of patients reported taking enoxaparin sodium and heparin sodium, respectively, subsequent to the first dose of ticagrelor). The YINGLONG study included patients already initiated on ticagrelor, and physicians may have selected patients with an anticipated low bleeding risk for ticagrelor treatment; i.e., a selection bias because the study was non-interventional and the treatment decision was made independently of any aspect of the study. By contrast, the non-interventional design would be expected to reduce risk for other types of bias seen in interventional, highly controlled studies with frequent visits and a free drug supply.

The lower rate of dyspnea (3.6%) in the YINGLONG study than that reported in the PLATO trial (13.8%) [16] or in the subgroup of East Asian patients (13.4%, 37/276) [17] in the PLATO trial could be accounted for by several factors. Because PLATO was conducted between 2006 and 2008 prior to ticagrelor's approval, and YINGLONG between 2015 and 2017 after ticagrelor's approval, patients with dyspnea—a known AE of ticagrelor—may have been less likely to accept participation in the YINGLONG study. Furthermore, cardiologists may have been less likely to initiate ticagrelor in patients with conditions associated with dyspnea. In PLATO, 15.1% of patients treated with ticagrelor had a history of dyspnea, whereas this information was not recorded in YINGLONG. Despite standardized training of investigators prior to study commencement in YINGLONG, under-reporting of events cannot be ruled out and may have also contributed to the lower rates of dyspnea observed in YINGLONG compared with PLATO. Intrinsic patient factors might also account for these differences, although there were proportionately similar numbers of females and patients aged greater than 75 years in both studies. However, the low number of Asian patients in PLATO prohibits any speculation. Dyspnea rates in YINGLONG were similar to those found in the PHILO study of patients with ACS from Japan, Taiwan, and South Korea, where the dyspnea rate was 5.7% (22/401) [20], and in the DAYU study [18], where the dyspnea rate was 3.4% (68/2001).

YINGLONG has several strengths and limitations. Consistent with the inherent nature of an observational study design and the lack of a control group, causality cannot be inferred. Events may have been under-reported, and, because of the low event rates, it is possible that a preponderance of low-risk patients was included. However, patient characteristics were mostly comparable with those of the PLATO trial, and similar to those seen in clinical practice, as well as other observational studies of patients with ACS in China [5, 20]. Although patients had to pay for ticagrelor in the YINGLONG study, the patients' possible differential ability to pay is unlikely to have influenced the results because in the acute stages the choice of treatment depends more on the severity of the disease. However, the impact of patients' ability to pay on treatment selection over the duration of the study cannot be excluded. A strength of the YINGLONG study is its prospective, non-interventional design, where the choice of treatment followed standard practice, which could increase external validity compared to a randomized controlled trial. Nonetheless, because the treatment was not randomized, unknown confounders could have influenced the results and causality between the intervention and the outcomes cannot be determined. In China, tertiary care hospitals represent the apex of medical care; thus, given the generalizability of our findings based on the study design, the results reported here can influence medical care at lower levels. However, the results may also not be applicable to all of China given the inclusion of only a limited number of tier 3 hospitals. It is therefore possible that the patients at these sites could differ from those in other hospitals throughout China. Moreover, because clopidogrel is commonly prescribed in China for patients with ACS, our results are particularly important given the high rates of cytochrome P450 family

2 subfamily C member 19 (*CYP2C19*) loss-of-function alleles present in Chinese patients [21–23], which increases the risk of adverse CV outcomes with clopidogrel [23, 24]. Chinese patients with ACS and *CYP2C19* loss-of-function alleles thus require alternative dual antiplatelet therapy, such as with ticagrelor. This underscores the value of having more data on ticagrelor in Chinese patients with ACS.

In conclusion, this real-world study provides further safety data on ticagrelor use for up to 1 year in Chinese patients with ACS, finding low rates of dyspnea and PLATO-defined bleeding events. The results are consistent with the known safety profile of ticagrelor, with no new safety findings.

ACKNOWLEDGEMENTS

The authors wish to thank the patients and investigators who participated in the YINGLONG study. A full list of the YINGLONG study investigators can be found in Supplementary File 4.

Funding. This study was funded by AstraZeneca Investment (China) Co., Ltd. AstraZeneca also funded the article processing charges for this manuscript and the open access fee. The sponsor did not influence the writing of the paper, other than employees of the sponsor who provided their professional input into the drafting and critique of the paper along with the other authors.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

Medical Writing, Editorial, and Other Assistance. Medical writing assistance, funded by AstraZeneca, was provided by Steven Tresker of Cactus Communications.

Disclosures. Chang-Sheng Ma received a research grant from AstraZeneca. Xin Du, Yang Zheng, Ping Yang, Shuren Ma, Zaixin Yu, Xi Su, Junbo Ge declare no conflicts of interest. Xianhong Wang is a current employee of AstraZeneca. Lu Bai is a current employee of AstraZeneca. Jing Sun is a current employee of AstraZeneca. Maria Leonsson-Zachrisson is a current employee of AstraZeneca.

Compliance with Ethics Guidelines. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation/Good Clinical Practice Guidelines and followed applicable regulatory requirements, including AstraZeneca's policy on bioethics. The local Institutional Review Boards or Independent Ethics Committees approved the final protocol and amendment.

Data Availability. Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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