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Time Course for Benefit and Risk of Ticagrelor and Aspirin in Acute Ischemic Stroke or Transient Ischemic Attack

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Abstract

Background and Objectives

The goal of this work was to investigate the short-term time-course benefit and risk of ticagrelor with aspirin in acute mild-moderate ischemic stroke or high-risk TIA in The Acute Stroke or Transient Ischemic Attack Treated with Ticagrelor and ASA for Prevention of Stroke and Death (THALES) trial.

Methods

In an exploratory analysis of the THALES trial, we evaluated the cumulative incidence of irreversible efficacy and safety outcomes at different time points during the 30-day treatment period. The efficacy outcome was major ischemic events defined as a composite of ischemic stroke or nonhemorrhagic death. The safety outcome was major hemorrhage defined as a composite of intracranial hemorrhage and fatal bleedings. Net clinical impact was defined as the combination of these 2 endpoints.

Results

This analysis included a total of 11,016 patients (5,523 in the ticagrelor-aspirin group, 5,493 in the aspirin group) with a mean age of 65 years, and 39% were women. The reduction of major ischemic events by ticagrelor occurred in the first week (4.1% vs 5.3%; absolute risk reduction 1.15%, 95% CI 0.36%–1.94%) and remained throughout the 30-day treatment period. An increase in major hemorrhage was seen during the first week and remained relatively constant in the following weeks (absolute risk increase ≈0.3%). Cumulative analysis showed that the net clinical impact favored ticagrelor-aspirin in the first week (absolute risk reduction 0.97%, 95% CI, 0.17%–1.77%) and remained constant throughout the 30 days.

Discussion

In patients with mild-moderate ischemic stroke or high-risk TIA, the treatment effect of ticagrelor-aspirin was present from the first week. The ischemic benefit of ticagrelor-aspirin outweighs the risk of major hemorrhage throughout the treatment period, which may support the use of 30-day treatment with ticagrelor and aspirin in these patients.

Classification of Evidence

This study provides Class II evidence that, for patients with mild-moderate ischemic stroke or high-risk TIA, the ischemic benefit of ticagrelor-aspirin outweighs the risk of major hemorrhage throughout the 30-day treatment period.

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Glossary

CHANCE = Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events; **DAPT** = dual antiplatelet therapy; **GUSTO** = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; **POINT** = Platelet Oriented Inhibition in New TIA and Minor Ischemic Stroke; **THALES** = The Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and ASA for Prevention of Stroke and Death.

Patients with minor ischemic stroke or TIA have a high short-term risk of subsequent stroke (≈4%–9% during the first 1–3 months).[1-3] Dual antiplatelet therapy (DAPT) started within 24 hours after symptom onset is an effective acute therapeutic strategy to reduce recurrent events for these patients.[4-7] The major concern in clinical practice is that DAPT may slightly increase the risk of major hemorrhage. This is a general concern with $P2Y_{12}$ inhibitors added to aspirin, including ticagrelor.

The Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and ASA for Prevention of Stroke and Death (THALES) trial[8] was a randomized trial that evaluated the efficacy and safety of DAPT with ticagrelor and aspirin vs aspirin alone in patients with mild to moderate acute ischemic stroke or TIA. The THALES trial demonstrated that, compared with aspirin alone, 30 days of DAPT with ticagrelor and aspirin reduced the risk of stroke and death but was associated with an increase in severe bleeding.[8] Due to their pharmacologic effects, long-term treatment with $P2Y_{12}$ inhibitors is associated with an increased risk of bleeding,[9] which has triggered interest in defining the duration of therapy with the best benefit-risk profile. A previous time-course analysis of the Platelet Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial demonstrated that the benefit of clopidogrel-aspirin occurs predominantly within the first 21 days, and limiting clopidogrel-aspirin use to 21 days may maximize benefit and reduce risk.[10] Whether a treatment period different from 30 days would improve benefit-risk of DAPT with ticagrelor and aspirin for mild to moderate stroke or TIA is unclear.

In this exploratory analysis of the THALES trial, we aimed to assess the time course of benefit and risk for 30-day treatment with ticagrelor-aspirin vs aspirin alone in patients with a mild to moderate acute ischemic stroke or TIA. The primary research question was whether the ischemic benefit and the risk of major hemorrhage of ticagrelor plus aspirin varied over time compared with aspirin alone in patients with mild-moderate ischemic stroke or high-risk TIA.

Methods

Study Participants

We used data from the THALES trial. Details on the design and primary results of the THALES trial have been published elsewhere.[8,11] In brief, THALES was an international, randomized, double-blind, placebo-controlled, parallel-group trial that randomized 11,016 patients from 414 sites in 28 countries between January 22, 2018, and December 13, 2019, to assess the efficacy and safety of combined treatment of ticagrelor (Brilinta, AstraZeneca Pharmaceuticals LP, Wilmington, DE) and aspirin vs aspirin alone in patients with acute ischemic stroke or TIA. Patients included in the trial were those ≥40 years of age and diagnosed with a mild to moderate acute noncardioembolic ischemic stroke (NIH Stroke Scale score ≤5 [range 0–42, with higher scores indicating more severe stroke]) or a high-risk TIA ($ABCD^2$ stroke risk score ≥6 [scores assessing the risk of stroke on the basis of age, blood pressure, clinical features, duration of TIA, and presence or absence of diabetes; range 0–7, with higher numbers indicating greater risk] or symptomatic intracranial or extracranial arterial stenosis [≥50% narrowing in the diameter of the lumen of an artery that could account for the TIA]) within 24 hours after symptom onset.[11]

Standard Protocol Approvals, Registrations, and Patient Consents

The THALES trial is registered at ClinicalTrials.gov (registration number NCT03354429). The protocol of the trial was approved by the ethics committee of all participating sites. All participants or their representatives provided written informed consent before enrollment.

Randomization and Treatments

We randomly assigned patients 1:1 to receive either ticagrelor (180 mg loading dose on day 1 followed by 90 mg twice daily on days 2–30) or matching placebo using an interactive web-based response system. All patients received aspirin (300–325 mg on day 1 followed by 75–100 mg daily on days 2–30).

Outcomes

We collected efficacy and safety outcomes through face-to-face interviews by trained site investigators, and all efficacy and safety analyses were based on investigator-assessed events.[8] Stroke events were classified as ischemic, hemorrhagic, or of undetermined cause; those of undetermined cause were analyzed as ischemic strokes. Bleeding events were classified as severe, moderate, or mild bleeding according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) definition.[8,12] The original primary efficacy outcome in the trial was the time from randomization to the first new stroke (ischemic or hemorrhagic) or death; the original safety outcome was the time to the first severe bleeding event according to the GUSTO definition (a composite of the first intracranial hemorrhage or fatal bleeding event or other bleeding that caused hemodynamic compromise requiring intervention).[8,12] In the present time-course benefit-risk analysis, we defined the efficacy outcome, major ischemic event, as the

composite of ischemic stroke or nonhemorrhagic death and defined the safety outcome, major hemorrhage, as intracranial hemorrhage or fatal bleedings. These endpoints represent irreversible harm and capture the expected main benefits and the most important possible risks expected for antiplatelet drugs while avoiding double counting of events.[13,14] Net clinical impact was defined as a composite of ischemic stroke, intracranial hemorrhage, fatal bleeding, and death, which included the combination of major ischemic events and major hemorrhage. In addition, moderate/severe bleeding events according to the GUSTO definition were assessed as a secondary safety outcome because this outcome is of significance in clinical practice and has been assessed in other antiplatelet trials.[3,15]

Statistical Analysis

All efficacy and safety analyses were performed by intention to treat according to the randomized treatment assignment regardless of the actual treatment received. Temporal course of risk differences of major ischemic events and major hemorrhage for ticagrelor vs placebo was presented graphically. We evaluated the cumulative incidence of major ischemic events, major hemorrhage, the composite of stroke or death, GUSTO severe bleeding, and GUSTO moderate/severe bleeding by treatment at different time points during 30-day follow-up (days 1–7, 1–14, 1–21, and 1–30). The number of events occurring during each cumulative time period was presented, and event rates were estimated from Kaplan-Meier percentages. The absolute risk difference in proportions (ticagrelor minus placebo) with their 95% CIs was calculated for each cumulative time period. Differences in time to the first event between treatment groups during each cumulative time period were evaluated with Cox proportional hazards regression models, and hazard ratios with their 95% CIs were reported for periods with at least 1 event in each treatment group.

Landmark analysis of ischemic benefit and hemorrhagic risk by week (days 1–7, 8–14, 15–21, and 22–30) was performed using the patients who were event-free at the start of each time period. Absolute risk difference in proportions and hazard ratios with their 95% CIs for ischemic benefit and hemorrhagic risk were also calculated for each time interval with at least 1 event in each treatment group. The cumulative analysis (primary analysis) evaluated the cumulative incidence of events at different time points, implicating the cumulative benefit and risk for different duration of DAPT, whereas the landmark analysis shows the events that occurred in each week, implicating the benefit and risk during each time interval.

Further analysis was conducted to estimate the treatment effect modeling a range of potential initiation times beyond 24 hours from symptom onset. Treatment differences in major ischemic events and major hemorrhages were estimated for every day from index event onset to 7 days. Censoring was left truncated, and patients with events before the given time period were removed.

All analyses presented were exploratory. No adjustment for multiple comparisons was made, and all p values were

Table 1 Baseline Characteristics of Included Patients

Characteristic	Ticagrelor (n = 5,523)	Placebo (n = 5,493)
Age, mean (SD), y	65.2 (11.0)	65.1 (11.1)
Female sex, n (%)	2,108 (38.2)	2,171 (39.5)
Race, n (%)		
White	2,973 (53.8)	2,948 (53.7)
Black	21 (0.4)	32 (0.6)
Asian	2,353 (42.6)	2,339 (42.6)
Other	176 (3.2)	174 (3.2)
Ethnic group, n (%)		
Hispanic or Latino	517 (9.4)	504 (9.2)
Not Hispanic or Latino	5,006 (90.6)	4,989 (90.8)
Region, n (%)		
Asia and Australia	2,373 (43.0)	2,356 (42.9)
Europe	2,814 (51.0)	2,803 (51.0)
North America	12 (0.2)	11 (0.2)
Central and South America	324 (5.9)	323 (5.9)
Body mass index, median (interquartile range), kg/m^2	25.9 (23.3–29.0)	25.7 (23.2–28.9)
Medical history, n (%)		
Current smoker	1,504 (27.2)	1,428 (26.0)
Hypertension	4,298 (77.8)	4,222 (76.9)
Diabetes (type 1 and 2)	1,589 (28.8)	1,557 (28.3)
Previous ischemic stroke	901 (16.3)	914 (16.6)
Previous TIA	275 (5.0)	240 (4.4)
Time from symptom onset to randomization <12 h, n (%)	1,812 (32.8)	1,776 (32.3)
Qualifying event, n (%)		
Ischemic stroke	5,032 (91.1)	4,953 (90.2)
TIA	491 (8.9)	540 (9.8)
ABCD^2 score in patients with qualifying TIA, n (%)		
≤5	60 (1.1)	71 (1.3)
6–7	431 (7.8)	469 (8.5)
NIHSS score in patients with qualifying ischemic stroke, n (%)		
≤3	3,359 (60.8)	3,312 (60.3)
>3	1,673 (30.3)	1,641 (29.9)

Abbreviations: ABCD^2 = age, blood pressure, clinical features, duration of TIA, and presence of diabetes mellitus; NIHSS = NIH Stroke Scale.

nominal. All analyses were performed with SAS software version 9.4 (SAS Institute Inc, Cary, NC).

Data Availability

The study protocol and statistical analysis plan were published elsewhere.[8] Data underlying the findings described here may be obtained in accordance with the AstraZeneca data-sharing policy.[16]

Results

A total of 11,016 patients with a mild-to-moderate ischemic stroke or a high-risk TIA were randomized in the THALES trial, including 5,523 patients in the ticagrelor group and 5,493 patients in the placebo group. All randomized patients were included in this analysis. The baseline characteristics of the included patients in each group are shown in Table 1.

Temporal course of risk differences of major ischemic events and major hemorrhage for ticagrelor vs placebo is presented in Figure 1. The curves for ischemic benefit and hemorrhagic risk diverge predominately in the first week, and then absolute differences remain constant throughout the 30 days. In the ticagrelor group, 291 (5.3%) major ischemic events and 22 (0.4%) major hemorrhages occurred within 30 days, with most events occurring in the first week. In the placebo group, 355 (6.5%) major ischemic events and 6 (0.1%) major hemorrhages occurred within 30 days, with most ischemic events also occurring in the first week but most hemorrhages occurring in later weeks (Table 2). Cumulative analysis showed that the reduction of major ischemic events by ticagrelor in the first week remained throughout the 30-day treatment period (absolute risk reduction ≈1.2%, with a number needed to treat of 84–90 for each time period) (Table 2). A similar trend was observed for the outcome of stroke or death. The absolute increase in major hemorrhage seen during the first week remained relatively constant in the following weeks (absolute risk increase ≈0.3%, with a number needed to harm of 324–367 for each time period). A similar trend was observed for GUSTO severe bleeding. The net clinical impact favored ticagrelor in the first week (absolute risk reduction 0.97%, 95% CI, 0.17%–1.77%) and remained constant throughout the 30 days.

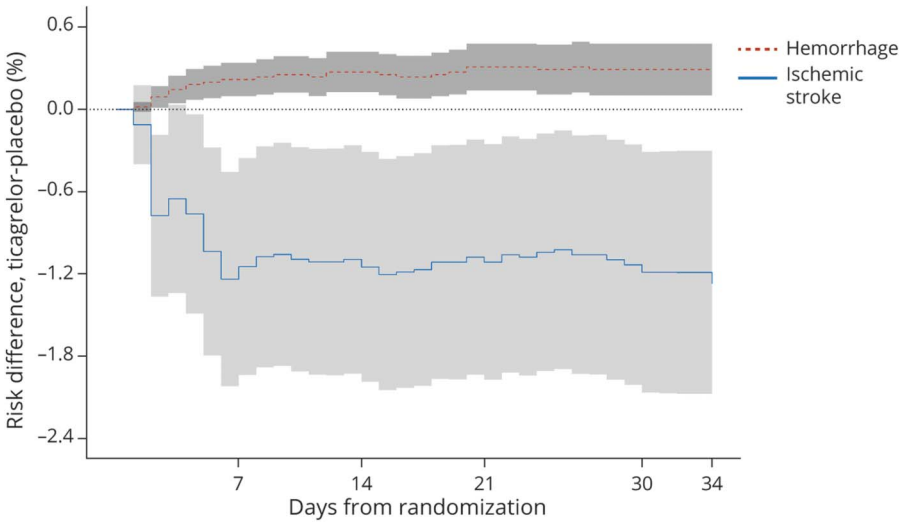
Landmark analysis showed that the largest reduction of major ischemic events by ticagrelor occurred in the first week (4.1% vs 5.3%, absolute risk reduction 1.15%, 95% CI 0.36%–1.94%) and attenuated but remained in the next 3 weeks (Table 3). A similar trend was observed for the outcome of stroke or death. Increase in major hemorrhage was low and relatively constant in the first 3 weeks but was not present in the last week. A similar trend was observed for GUSTO severe bleeding and moderate to severe bleeding.

In analyses of treatment effect that modeled time to initiation of treatment beyond 24 hours, the absolute risk of ischemic events remained lower in the ticagrelor group even when it was initiated days after symptom onset (Figure 2). The benefit of ticagrelor was greatest when initiated within 1 day of symptom onset, but the risk difference indicated that ticagrelor could potentially be effective if initiated 5 days after onset. The absolute risk of hemorrhage was small and significant when ticagrelor was initiated within 3 days after onset but not significant when initiated from 4 days after onset (Figure 2).

Classification of Evidence

This study provides Class II evidence that, for patients with mild-moderate ischemic stroke or high-risk TIA, the ischemic

Figure 1 Temporal Course of Risk Difference for Ticagrelor vs Placebo



Dashed red line indicates risk difference of major hemorrhage; solid blue line indicates risk difference of major ischemic event. Shadings indicate 95% CIs. Major ischemic event was defined as the composite of ischemic stroke or nonhemorrhagic death. Major hemorrhage was defined as intracranial hemorrhage or fatal bleedings.

Table 2 Cumulative Analysis of Benefit and Risk at Different Time Points up to 30 Days

		Ticagrelor (n = 5,523)			Placebo (n = 5,493)					
Outcome	Time interval	No.	Patients with events, n (%)	KM% (end of interval)	No.	Patients with events, n (%)	KM% (end of interval)	Risk difference (95% CI), %	Hazard ratio (95% CI)	*p* Value
Net clinical impact[a]	Day 1–7	5,523	238 (4.3)	4.3	5,493	290 (5.3)	5.3	−0.97 (−1.77, −0.17)	0.81 (0.68, 0.96)	0.02
	Day 1–14	5,523	275 (5.0)	5.0	5,493	324 (5.9)	5.9	−0.92 (−1.76, −0.07)	0.84 (0.72, 0.99)	0.03
	Day 1–21	5,523	295 (5.3)	5.3	5,493	340 (6.2)	6.2	−0.84 (−1.72, 0.03)	0.86 (0.73, 1.00)	0.056
	Day 1–30	5,523	308 (5.6)	5.6	5,493	360 (6.6)	6.6	−0.97 (−1.87, −0.08)	0.85 (0.73, 0.99)	0.03
Major ischemic event[b]	Day 1–7	5,523	228 (4.1)	4.1	5,493	290 (5.3)	5.3	−1.15 (−1.94, −0.36)	0.78 (0.65, 0.93)	0.005
	Day 1–14	5,523	262 (4.7)	4.8	5,493	324 (5.9)	5.9	−1.15 (−1.99, −0.31)	0.80 (0.68, 0.94)	0.007
	Day 1–21	5,523	278 (5.0)	5.0	5,493	338 (6.2)	6.2	−1.11 (−1.97, −0.26)	0.81 (0.69, 0.95)	0.01
	Day 1–30	5,523	291 (5.3)	5.3	5,493	355 (6.5)	6.5	−1.19 (−2.07, −0.31)	0.81 (0.69, 0.95)	0.008
Major hemorrhage[c]	Day 1–7	5,523	12 (0.2)	0.2	5,493	0 (0.0)		NA	NA	NA
	Day 1–14	5,523	16 (0.3)	0.3	5,493	1 (0.0)	0.0	0.27 (0.13, 0.42)	15.94 (2.12, 120.13)	0.007
	Day 1–21	5,523	20 (0.4)	0.4	5,493	3 (0.1)	0.1	0.31 (0.14, 0.48)	6.65 (1.98, 22.37)	0.002
	Day 1–30	5,523	22 (0.4)	0.4	5,493	6 (0.1)	0.1	0.29 (0.10, 0.48)	3.66 (1.48, 9.02)	0.005
Stroke or death	Day 1–7	5,523	233 (4.2)	4.2	5,493	290 (5.3)	5.3	−1.06 (−1.85, −0.26)	0.80 (0.67, 0.95)	0.009
	Day 1–14	5,523	269 (4.9)	4.9	5,493	324 (5.9)	5.9	−1.02 (−1.87, −0.18)	0.82 (0.70, 0.97)	0.02
	Day 1–21	5,523	287 (5.2)	5.2	5,493	338 (6.2)	6.2	−0.95 (−1.82, −0.09)	0.84 (0.72, 0.98)	0.03
	Day 1–30	5,523	300 (5.4)	5.4	5,493	358 (6.5)	6.5	−1.08 (−1.97, −0.20)	0.83 (0.71, 0.97)	0.02
GUSTO severe bleeding	Day 1–7	5,523	16 (0.3)	0.3	5,493	0 (0.0)		NA	NA	NA
	Day 1–14	5,523	21 (0.4)	0.4	5,493	2 (0.0)	0.0	0.34 (0.17, 0.52)	10.47 (2.46, 44.66)	0.002
	Day 1–21	5,523	25 (0.5)	0.5	5,493	4 (0.1)	0.1	0.38 (0.19, 0.57)	6.23 (2.17, 17.90)	<0.001
	Day 1–30	5,523	28 (0.5)	0.5	5,493	7 (0.1)	0.1	0.38 (0.17, 0.59)	3.99 (1.74, 9.14)	0.001
GUSTO moderate/ severe bleeding	Day 1–7	5,523	16 (0.3)	0.3	5,493	1 (0.0)	0.0	0.27 (0.13, 0.42)	15.94 (2.11, 120.13)	0.007
	Day 1–14	5,523	26 (0.5)	0.5	5,493	4 (0.1)	0.1	0.40 (0.20, 0.59)	6.48 (2.26, 18.58)	<0.001
	Day 1–21	5,523	32 (0.6)	0.6	5,493	6 (0.1)	0.1	0.47 (0.25, 0.69)	5.32 (2.22, 12.72)	<0.001
	Day 1–30	5,523	35 (0.6)	0.6	5,493	10 (0.2)	0.2	0.45 (0.21, 0.69)	3.49 (1.73, 7.06)	<0.001

Abbreviations: GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; KM = Kaplan-Meier; NA = not applicable.
[a] Net clinical impact was defined as a composite of ischemic stroke, intracranial hemorrhage, fatal bleeding, and death.
[b] Major ischemic event was defined as the composite of ischemic stroke or nonhemorrhagic death.
[c] Major hemorrhage was defined as intracranial hemorrhage or fatal bleedings.

benefit of ticagrelor-aspirin outweighs the risk of major hemorrhage throughout the 30-day treatment period.

Discussion

In this post hoc exploratory analysis of the THALES trial, we found that ticagrelor-aspirin treatment in patients with mild to moderate acute ischemic stroke or TIA reduced the risk of major ischemic events predominately in the first week, an effect that persisted throughout the 30-day period, with a low and constant increase of major hemorrhage from the first week to the following weeks. The net clinical impact favored ticagrelor-aspirin treatment in the first week, an effect that persisted during the entire 30-day treatment

Table 3 Landmark Analysis of Benefit and Risk by Week After Randomization

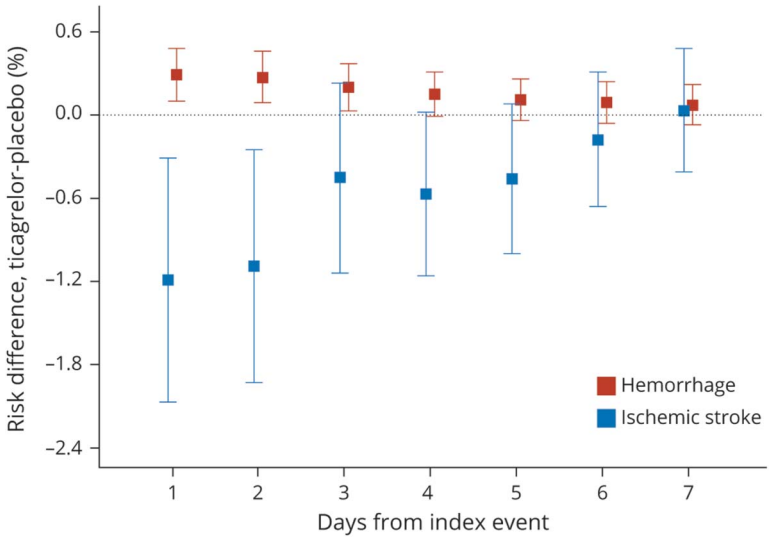
		Ticagrelor (n = 5,523)			Placebo (n = 5,493)					
Outcome	**Time interval**	**No.**	**Patients with events, n (%)**	**KM% (end of interval)**	**No.**	**Patients with events, n (%)**	**KM% (end of interval)**	**Risk difference (95% CI), %**	**Hazard ratio (95% CI)**	***p* Value**
Net clinical impact[a]	Day 1–7	5,523	238 (4.3)	4.3	5,493	290 (5.3)	5.3	−0.97 (−1.77, −0.17)	0.81 (0.68, 0.96)	0.02
	Day 8–14	5,273	37 (0.7)	0.7	5,199	34 (0.7)	0.7	0.05 (−0.27, 0.36)	1.07 (0.67, 1.71)	0.77
	Day 15–21	5,235	20 (0.4)	0.4	5,159	16 (0.3)	0.3	0.07 (−0.15, 0.30)	1.23 (0.64, 2.38)	0.54
	Day 22–30	5,214	13 (0.2)	0.2	5,141	20 (0.4)	0.4	−0.14 (−0.36, 0.08)	0.64 (0.32, 1.29)	0.21
Major ischemic event[b]	Day 1–7	5,523	228 (4.1)	4.1	5,493	290 (5.3)	5.3	−1.15 (−1.94, −0.36)	0.78 (0.65, 0.93)	0.005
	Day 8–14	5,278	34 (0.6)	0.6	5,197	34 (0.7)	0.7	−0.01 (−0.32, 0.30)	0.98 (0.61, 1.58)	0.95
	Day 15–21	5,241	16 (0.3)	0.3	5,157	14 (0.3)	0.3	0.03 (−0.17, 0.24)	1.12 (0.55, 2.30)	0.75
	Day 22–30	5,224	13 (0.2)	0.2	5,141	17 (0.3)	0.3	−0.08 (−0.29, 0.13)	0.75 (0.37, 1.55)	0.44
Major hemorrhage[c]	Day 1–7	5,523	12 (0.2)	0.2	5,493	0 (0.0)		NA	NA	NA
	Day 8–14	5,481	4 (0.1)	0.1	5,473	1 (0.0)	0.0	0.05 (−0.03, 0.13)	3.99 (0.45, 35.72)	0.22
	Day 15–21	5,470	4 (0.1)	0.1	5,460	2 (0.0)	0.0	0.04 (−0.05, 0.12)	2.00 (0.37, 10.90)	0.43
	Day 22–30	5,463	2 (0.0)	0.0	5,455	3 (0.1)	0.1	−0.02 (−0.10, 0.06)	0.67 (0.11, 3.98)	0.66
Stroke or death	Day 1–7	5,523	233 (4.2)	4.2	5,493	290 (5.3)	5.3	−1.06 (−1.85, −0.26)	0.80 (0.67, 0.95)	0.009
	Day 8–14	5,278	36 (0.7)	0.7	5,199	34 (0.7)	0.7	0.03 (−0.28, 0.34)	1.04 (0.65, 1.67)	0.86
	Day 15–21	5,241	18 (0.3)	0.3	5,159	14 (0.3)	0.3	0.07 (−0.14, 0.28)	1.27 (0.63, 2.54)	0.51
	Day 22–30	5,222	13 (0.2)	0.2	5,143	20 (0.4)	0.4	−0.14 (−0.36, 0.08)	0.64 (0.32, 1.29)	0.21
GUSTO severe bleeding	Day 1–7	5,523	16 (0.3)	0.3	5,493	0 (0.0)		NA	NA	NA
	Day 8–14	5,478	5 (0.1)	0.1	5,473	2 (0.0)	0.0	0.05 (−0.04, 0.15)	2.50 (0.48, 12.87)	0.27
	Day 15–21	5,467	4 (0.1)	0.1	5,459	2 (0.0)	0.0	0.04 (−0.05, 0.12)	2.00 (0.37, 10.90)	0.43
	Day 22–30	5,460	3 (0.1)	0.1	5,454	3 (0.1)	0.1	−0.00 (−0.09, 0.09)	1.00 (0.20, 4.95)	>0.99
GUSTO moderate/ severe bleeding	Day 1–7	5,523	16 (0.3)	0.3	5,493	1 (0.0)	0.0	0.27 (0.13, 0.42)	15.94 (2.11, 120.13)	0.007
	Day 8–14	5,478	10 (0.2)	0.2	5,472	3 (0.1)	0.1	0.13 (−0.00, 0.26)	3.33 (0.92, 12.10)	0.07
	Day 15–21	5,462	6 (0.1)	0.1	5,457	2 (0.0)	0.0	0.07 (−0.03, 0.17)	3.00 (0.60, 14.85)	0.18
	Day 22–30	5,453	3 (0.1)	0.1	5,452	4 (0.1)	0.1	−0.02 (−0.11, 0.08)	0.75 (0.17, 3.35)	0.71

Abbreviations: GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; KM = Kaplan-Meier; NA = not applicable.
[a] Net clinical impact was defined as a composite of ischemic stroke, intracranial hemorrhage, fatal bleeding, and death.
[b] Major ischemic event was defined as the composite of ischemic stroke or nonhemorrhagic death.
[c] Major hemorrhage was defined as intracranial hemorrhage or fatal bleedings.

period. This finding supports treating for the full 30-day course of DAPT with ticagrelor and aspirin as originally tested in the trial, which is consistent with the recent guideline from the American Heart Association/American Stroke Association[4] and a European Stroke Organization expedited recommendation.[7]

Besides a reduction in the risk of recurrent ischemic events, antiplatelet drugs are associated with a small but relevant increased risk of serious bleeding.[17] Increased risk of bleeding is the major concern when prolonged intensive antiplatelet therapy is administrated in clinical practice.[18] A shortened duration of DAPT may reduce the risk of bleeding.[19] Recent meta-analyses indicated that short-term (within 1 month) DAPT may decrease the risk of recurrent stroke without increasing the risk of hemorrhage compared to monotherapy in patients with ischemic stroke or TIA.[20,21] In the prespecified secondary analysis of the POINT trial, DAPT with clopidogrel

Figure 2 Impact of Timing of the Initiation of Treatment



Effect of timing of initiating ticagrelor treatment on cumulative probability of events at 30 days was modeled. Red line indicates risk difference of major hemorrhage; blue line indicates risk difference of major ischemic event at various times after symptom onset. Vertical lines indicate 95% CIs.

and aspirin was more beneficial for 7-day and 30-day treatment courses compared to the full 90-day treatment period evaluated in the trial.[22] The secondary analysis of the POINT trial[10] and the pooled analysis of the Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events (CHANCE) and POINT trials[3] demonstrated that the benefit of DAPT with clopidogrel and aspirin was confined to the first 21 days after minor ischemic stroke or high-risk TIA and that prolonged DAPT may increase hemorrhagic risk without additional ischemic benefit.

Platelet activation remains elevated in patients for at least 1 month after an acute ischemic stroke or TIA, although the exact duration is uncertain.[23,24] During this period, more intense antiplatelet treatment is warranted. Ticagrelor is a potent antiplatelet agent that reversibly binds and inhibits the $P2Y_{12}$ receptor on platelets. In contrast to clopidogrel, it is direct acting without requirement of metabolic activation.[25] However, the efficacy benefit of intensive DAPT with ticagrelor and aspirin may come at a cost of a small increase in bleeding. No previous study has investigated the temporal course of benefit and risk to attempt to define an optimal duration of ticagrelor-aspirin treatment in patients with acute ischemic stroke or TIA. In addition to the overall benefit and risk of ticagrelor-aspirin treatment in the THALES trial,[14] the results of the present study suggest that the treatment benefit of ticagrelor-aspirin occurs predominantly in the first week and remains during the entire 30-day period. Although the present analysis indicated that ticagrelor treatment, even if initiated 5 days after event onset, may still be beneficial, it should not discourage emergent treatment whenever possible. In addition, the findings of initiation time of ticagrelor treatment should be considered cautiously because they are based on post hoc exploratory analysis of modeled results.

This study has several limitations. First, this secondary analysis on treatment pattern over time is exploratory and thus does not meet the standards of evidence of a primary clinical trial. All patients were randomized to 30-day treatment. The impact of stopping treatment earlier than 30 days has not been investigated. Moreover, the landmark analyses are hampered by low power, especially for the hemorrhagic events. To validate optimal treatment duration, dedicated randomized trials would be needed, and they would need to be large. Second, treatment discontinuation was somewhat higher in the ticagrelor-aspirin group compared with the aspirin alone group (14.3% vs 11.7%). This may result in underestimation of ischemic benefit of ticagrelor-aspirin group. Third, this trial enrolled a mostly White and Asian population with very few participants from different racial or ethnic groups. Caution is needed when the findings are generalized.

This analysis suggests that the ischemic benefit of ticagrelor-aspirin treatment outweighs the risk of major hemorrhage throughout the 30-day treatment period in patients with mild-moderate ischemic stroke or high-risk TIA. The treatment benefit of ticagrelor-aspirin occurs predominantly in the first week and remains during the entire 30-day period. This analysis does not support shortening the 30-day regimen of DAPT with ticagrelor and aspirin, and a shorter treatment period has not been studied.

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Time Course for Benefit and Risk of Ticagrelor and Aspirin in Acute Ischemic Stroke or Transient Ischemic Attack

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