

# Efficacy and Safety of Ticagrelor and Aspirin in Patients With Moderate Ischemic Stroke

## An Exploratory Analysis of the THALES Randomized Clinical Trial

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 Supplemental content

**IMPORTANCE** Prior trials of dual antiplatelet therapy excluded patients with moderate ischemic stroke. These patients were included in the Acute Stroke or Transient Ischaemic Attack Treated With Ticagrelor and ASA for Prevention of Stroke and Death (THALES) trial, but results have not been reported separately, raising concerns about safety and efficacy in this subgroup.

**OBJECTIVE** To evaluate the efficacy and safety of ticagrelor plus aspirin in patients with moderate ischemic stroke (National Institutes of Health Stroke Scale [NIHSS] score of 4 to 5).

**DESIGN, SETTING, AND PARTICIPANTS** The THALES trial was a randomized trial conducted at 414 hospitals in 28 countries in January 2018 and December 2019. This exploratory analysis compared patients with moderate stroke (baseline NIHSS score of 4 to 5) with patients with less severe stroke (NIHSS score of 0 to 3). A total of 9983 patients with stroke were included in the present analysis, after excluding 2 patients with NIHSS scores greater than 5 and 1031 patients with transient ischemic attack. Data were analyzed from March to April 2021.

**INTERVENTIONS** Ticagrelor (180-mg loading dose on day 1 followed by 90 mg twice daily on days 2 to 30) or placebo within 24 hours after symptom onset. All patients received aspirin, 300 to 325 mg, on day 1 followed by aspirin, 75 to 100 mg, daily on days 2 to 30. Patients were observed for 30 additional days.

**MAIN OUTCOMES AND MEASURES** The primary outcome was time to stroke or death within 30 days. The primary safety outcome was time to severe bleeding.

**RESULTS** In total, 3312 patients presented with moderate stroke and 6671 presented with less severe stroke. Of those in the moderate stroke group, 1293 (39.0%) were female, and the mean (SD) age was 64.5 (10.8) years; of those in the less severe stroke group, 2518 (37.7%) were female, and the mean (SD) age was 64.8 (11.2) years. The observed primary outcome event rate in patients with moderate stroke was 7.6% (129 of 1671) for those in the ticagrelor group and 9.1% (150 of 1641) for those in the placebo group (hazard ratio, 0.84; 95% CI, 0.66-1.06); the primary outcome event rate in patients with less severe stroke was 4.7% (158 of 3359) for those in the ticagrelor group and 5.7% (190 of 3312) for those in the placebo group (hazard ratio, 0.82; 95% CI, 0.66-1.01) (*P* for interaction = .88). Severe bleeding occurred in 8 patients (0.5%) in the ticagrelor group and in 4 patients (0.2%) in the placebo group in those with moderate stroke compared with 16 patients (0.5%) and 3 patients (0.1%), respectively, with less severe stroke (*P* for interaction = .26).

**CONCLUSIONS AND RELEVANCE** In this study, patients with a moderate ischemic stroke had consistent benefit from ticagrelor plus aspirin vs aspirin alone compared with patients with less severe ischemic stroke, with no further increase in the risk of intracranial bleeding or other severe bleeding events.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier: [NCT03354429](https://clinicaltrials.gov/ct2/show/study/NCT03354429)

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Dual antiplatelet therapy (DAPT) is a pivotal strategy for early management of minor noncardioembolic ischemic stroke and transient ischemic attack (TIA).<sup>1-4</sup> The efficacy and safety of DAPT with clopidogrel and aspirin have been evaluated in patient populations with TIA or acute ischemic stroke with baseline National Institutes of Health Stroke Scale (NIHSS) scores of 3 or less (range, 0-42; higher scores indicate more severe stroke) in the Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events (CHANCE) trial<sup>5</sup> and Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial.<sup>6</sup> Based on these studies, the current guidelines recommend early, short (21 days) combination treatment with clopidogrel and aspirin for patients with high-risk TIA and minor noncardioembolic ischemic stroke with an NIHSS score of 3 or less.<sup>1,2,4</sup>

In the Acute Stroke or Transient Ischaemic Attack Treated With Ticagrelor and ASA for Prevention of Stroke and Death (THALES) trial,<sup>7</sup> DAPT with ticagrelor and aspirin was evaluated in patients with TIA or acute ischemic stroke with NIHSS scores of 5 or less, within which approximately 30% of the patient population had NIHSS scores of 4 or 5 at randomization. The THALES trial demonstrated that compared with aspirin alone, DAPT with ticagrelor and aspirin reduced the risk of stroke or death within 30 days. Few severe bleeding events were observed; however, these were more common in the ticagrelor plus aspirin group.<sup>7</sup> Patients with stroke with baseline NIHSS scores of 4 to 5 could potentially respond differently than those with an NIHSS score of 0 to 3 to DAPT, owing to more severe neurological impairment and larger areas of ischemic injury, eg, they may have a greater risk of brain hemorrhage. To our knowledge, no randomized trials have previously evaluated the efficacy and safety of DAPT in patients with moderate stroke (NIHSS score of 4 to 5), and whether the benefit of DAPT can extend to patients with ischemic stroke with a severity of NIHSS score 4 to 5 has rendered interest from stroke neurologists. In this exploratory subgroup analysis of the THALES trial, we aimed to characterize the efficacy and safety of DAPT with ticagrelor plus aspirin in the first 30 days in patients with an acute ischemic stroke with a baseline NIHSS score of 4 or 5.

## Methods

### Overview of the THALES Trial

Details on the rationale, design, and main results of the THALES trial have been published previously.<sup>7,8</sup> The THALES trial was a multicenter, double-blind, placebo-controlled, parallel-group randomized clinical trial, which was sponsored by AstraZeneca and conducted at 414 sites in 28 countries between January 22, 2018, and December 13, 2019. The objective of the THALES trial was to compare the efficacy and safety of ticagrelor (180-mg loading dose on day 1 followed by 90 mg twice daily on days 2 to 30) with placebo in patients with acute minor noncardioembolic ischemic stroke or TIA. All patients took aspirin (300 to 325 mg on day 1 followed by 75 to 100 mg daily on days 2 to 30) in the first 30 days. The trial was approved by the ethics committee at each participating site.

### Key Points

**Question** Is dual antiplatelet therapy with ticagrelor plus aspirin of benefit for patients with moderate acute ischemic stroke (National Institutes of Health Stroke Scale [NIHSS] score of 4 to 5)?

**Findings** In this exploratory post-hoc analysis of the THALES trial including 9983 patients with moderate or less severe stroke (NIHSS score of 0 to 3), treatment with ticagrelor plus aspirin showed similar efficacy and safety vs aspirin alone among patients presenting with moderate acute ischemic stroke and those presenting with less severe ischemic cerebrovascular events.

**Meaning** Patients with moderate ischemic stroke may benefit from dual antiplatelet therapy with ticagrelor and aspirin.

Written informed consent was obtained from all the participants or their representatives before enrollment. The trial protocol can be found in [Supplement 1](#).

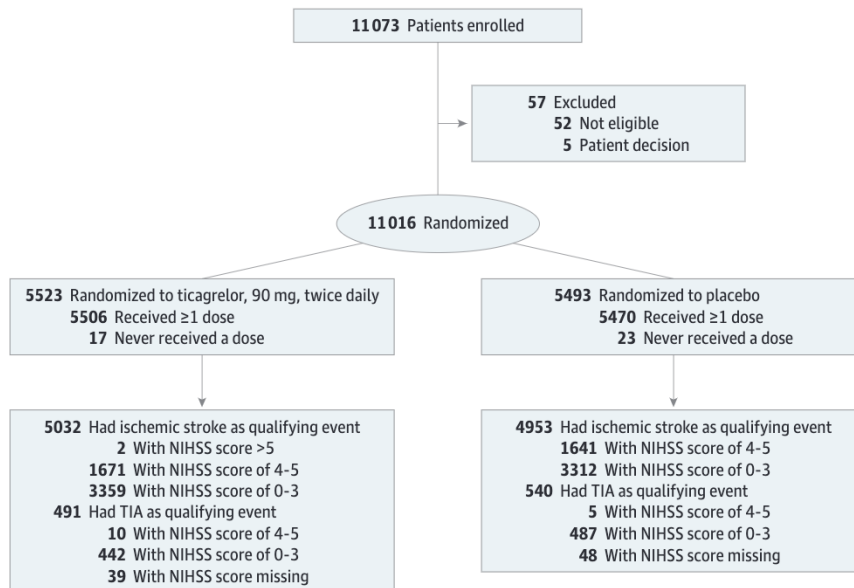
Patients eligible for inclusion in the THALES trial were 40 years or older, had an acute noncardioembolic ischemic stroke with an NIHSS score of 5 or less or a high-risk TIA (ABCD<sup>2</sup> stroke risk score [scores assessing the risk of stroke on the basis of age, blood pressure, clinical features, duration of TIA, and presence or absence of diabetes; range, 0 to 7] of 6 or greater or symptomatic intracranial or extracranial arterial stenosis [50% or greater narrowing in the diameter of the lumen of an artery that could account for the TIA]), and could undergo randomization within 24 hours after symptom onset. Participants' race was classified by investigators, and options for race were prespecified. Participant race was included as part of an initiative to ensure that a variety of nationalities, ethnicities and races were represented, that the results of the study would be widely applicable, and to allow for subgroup analysis of patients by race in a Cox proportional hazards model. Detailed information on inclusion and exclusion criteria is provided in the study protocol.<sup>7,8</sup>

An exploratory analysis of data from patients with stroke with a baseline NIHSS score of 4 to 5 who participated in the THALES trial was performed and reported in this article. This analysis was performed to compare patients with moderate stroke (baseline NIHSS score of 4 to 5) with those with less severe stroke (baseline NIHSS score of 0 to 3) among patients with ischemic stroke as a qualifying event as the main analysis and among the entire population regardless of qualifying event (ischemic stroke or TIA) as a sensitivity analysis.

### Outcomes

The primary efficacy outcome was time from randomization to the first occurrence of new stroke (ischemic or hemorrhagic) or death within 30 days. Stroke events included both progression of index stroke (defined by rapid worsening of an existing focal neurological deficit attributable to a new infarction or extension of a previous infarction in the same vascular bed) or new stroke events (including ischemic, hemorrhagic, and undetermined strokes). Death included all causes of death. The secondary outcomes included time to first subsequent ischemic stroke within 30 days and overall disability measured as a modified Rankin Scale (mRS) score greater than

Figure 1. Flow Diagram



1 at the end-of-treatment visit 30 to 34 days after randomization. Disabling stroke (subsequent stroke with an mRS score greater than 1 at day 30) was an exploratory end point. The safety outcomes included time to first severe bleeding event according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) definition,<sup>7,9</sup> a composite of the first intracranial hemorrhage or fatal bleeding event, the first moderate or severe bleeding event according to the GUSTO definition, and premature permanent discontinuation of study drugs because of bleeding. All efficacy and safety analyses were based on investigator-assessed events.<sup>7</sup> The definitions of stroke, death, disability, and bleeding outcomes in the THALES trial have been reported previously.<sup>7</sup>

### Statistical Analysis

This post hoc analysis was exploratory and hypothesis generating across prespecified subgroups. Baseline characteristics were presented by antiplatelet treatment groups (ticagrelor or placebo) and baseline NIHSS groups (NIHSS score of 0 to 3 vs 4 to 5). Categorical variables were presented as percentages and continuous variables as medians with interquartile ranges or means with standard deviations, as appropriate.

All efficacy and safety analyses were based on the intention-to-treat principle and included all randomized patients. Interaction between treatment assignment on all outcomes and baseline NIHSS groups were evaluated by including terms for treatment assignment (ticagrelor or placebo), baseline NIHSS group (NIHSS score of 0 to 3 or 4 to 5), and treatment × NIHSS group interaction as covariates in Cox or logistic regression models. Interaction terms with a 2-tailed *P* value less than .05 were considered statistically significant. For outcomes of stroke or death, ischemic stroke, and bleeding events, we estimated event rates by Kaplan-Meier method and presented the time to the first event using Kaplan-Meier curves

(1 – proportion free of event). Differences in time to the first events between study groups within the NIHSS subgroups were evaluated using Cox proportional hazards regression models, and hazard ratios (HRs) were reported with 95% CIs. For the outcome of overall disability and disabling stroke, differences between study groups within the baseline NIHSS groups were evaluated using logistic regression models, and odds ratios (ORs) with their 95% CIs are reported.

With 279 primary events in the moderate stroke group (baseline NIHSS score of 4 to 5), the power was 31% to detect an effect with an HR of 0.84. No adjustment for multiple comparisons was made, and all *P* values were nominal, since all analyses presented were exploratory. All analyses were performed with SAS software version 9.4 (SAS Institute).

## Results

### Study Participants

For the present subgroup analysis, 9983 patients with stroke were included of the 11 016 randomized patients in the THALES trial, including 3312 patients (30.1%) with moderate stroke and 6671 patients (60.6%) with less severe stroke, excluding 2 patients with stroke with an NIHSS score greater than 5 and 1031 patients with TIA (Figure 1). Of those in the moderate stroke group, 1293 (39.0%) were female, and the mean (SD) age was 64.5 (10.8) years; of those in the less severe stroke group, 2518 (37.7%) were female, and the mean (SD) age was 64.8 (11.2) years. Among the 3312 patients with moderate stroke, 1671 patients were assigned to the ticagrelor group and 1641 to the placebo group. Baseline characteristics of patients with baseline NIHSS scores of 0 to 3 and 4 to 5 among those with ischemic stroke as a qualifying event and those in the entire population are presented in Table 1 and eTable 1 in Supplement 2, respectively. Compared with those with baseline NIHSS scores



**Table 1. Baseline Characteristics of Included Patients With Stroke by Baseline National Institutes of Health Stroke Scale (NIHSS) Group**

Characteristic	No. (%)					
	NIHSS score of 0-3			NIHSS score of 4-5		
	Ticagrelor (n = 3359)	Placebo (n = 3312)	Total (n = 6671)	Ticagrelor (n = 1671)	Placebo (n = 1641)	Total (n = 3312)
Age, mean (SD), y	65.0 (11.1)	64.6 (11.3)	64.8 (11.2)	64.4 (10.8)	64.6 (10.8)	64.5 (10.8)
Female	1237 (36.8)	1281 (38.7)	2518 (37.7)	650 (38.9)	643 (39.2)	1293 (39.0)
Race						
White	1765 (52.5)	1711 (51.7)	3476 (52.1)	866 (51.8)	873 (53.2)	1739 (52.5)
Black	15 (0.4)	19 (0.6)	34 (0.5)	4 (0.2)	9 (0.5)	13 (0.4)
Asian	1529 (45.5)	1526 (46.1)	3055 (45.8)	703 (42.1)	668 (40.7)	1371 (41.4)
Other	50 (1.5)	56 (1.7)	106 (1.6)	98 (5.9)	91 (5.5)	189 (5.7)
Region						
Asia and Australia	1546 (46.0)	1536 (46.4)	3082 (46.2)	704 (42.1)	665 (40.5)	1369 (41.3)
Europe	1652 (49.2)	1624 (49.0)	3276 (49.1)	844 (50.5)	846 (51.6)	1690 (51.0)
North America	7 (0.2)	6 (0.2)	13 (0.2)	1 (0.1)	2 (0.1)	3 (0.1)
Central and South America	154 (4.6)	146 (4.4)	300 (4.5)	122 (7.3)	128 (7.8)	250 (7.5)
Blood pressure, median (IQR), mm Hg						
Systolic	148.0 (132.0-161.0)	147.0 (132.0-160.0)	148.0 (132.0-160.0)	150.0 (138.5-166.0)	150.0 (135.0-167.0)	150.0 (137.0-166.0)
Diastolic	82.0 (78.0-91.0)	83.0 (77.0-91.0)	83.0 (78.0-91.0)	85.0 (80.0-92.0)	85.0 (80.0-91.0)	85.0 (80.0-92.0)
Body mass index, median (IQR) <sup>a</sup>	25.7 (23.2-28.9)	25.6 (23.1-28.7)	25.7 (23.1-28.7)	26.0 (23.2-29.1)	25.8 (23.2-29.3)	25.9 (23.2-29.1)
Medical history						
Current smoker	937 (27.9)	860 (26.0)	1797 (26.9)	475 (28.4)	466 (28.4)	941 (28.4)
Hypertension	2524 (75.1)	2416 (72.9)	4940 (74.1)	1370 (82.0)	1343 (81.8)	2713 (81.9)
Dyslipidemia	1278 (38.0)	1182 (35.7)	2460 (36.9)	627 (37.5)	614 (37.4)	1241 (37.5)
Diabetes (type 1 and 2)	872 (26.0)	846 (25.5)	1718 (25.8)	483 (28.9)	455 (27.7)	938 (28.3)
Prior ischemic heart disease	309 (9.2)	301 (9.1)	610 (9.1)	169 (10.1)	169 (10.3)	338 (10.2)
Congestive heart failure	104 (3.1)	103 (3.1)	207 (3.1)	85 (5.1)	86 (5.2)	171 (5.2)
Previous ischemic stroke	524 (15.6)	547 (16.5)	1071 (16.1)	308 (18.4)	272 (16.6)	580 (17.5)
Previous TIA	128 (3.8)	107 (3.2)	235 (3.5)	57 (3.4)	49 (3.0)	106 (3.2)
Taking aspirin prior to index event	476 (14.2)	401 (12.1)	877 (13.1)	184 (11.0)	159 (9.7)	343 (10.4)
Taking clopidogrel prior to index event	49 (1.5)	53 (1.6)	102 (1.5)	15 (0.9)	10 (0.6)	25 (0.8)
Time from symptom onset to randomization, h						
<12	1145 (34.1)	1109 (33.5)	2254 (33.8)	460 (27.5)	448 (27.3)	908 (27.4)
≥12	2214 (65.9)	2203 (66.5)	4417 (66.2)	1211 (72.5)	1193 (72.7)	2404 (72.6)
Qualifying event						
Ischemic stroke	3359 (100)	3312 (100)	6671 (100)	1671 (100)	1641 (100)	3312 (100)
TIA	0	0	0	0	0	0
Persistent signs or symptoms at the time of randomization	3233 (96.2)	3157 (95.3)	6390 (95.8)	1670 (99.9)	1641 (100)	3311 (100)
Acute ischemic brain lesion at the time of randomization	1633 (48.6)	1655 (50.0)	3288 (49.3)	875 (52.4)	835 (50.9)	1710 (51.6)

Abbreviations: IQR, interquartile range; TIA, transient ischemic attack.

<sup>a</sup> Calculated as weight in kilograms divided by height in meters squared.

of 0 to 3, patients with NIHSS scores of 4 to 5 were less likely to be Asian, to take aspirin and clopidogrel prior to the index event, and to be randomized within 12 hours from symptom onset but more likely to have hypertension, diabetes, and congestive heart failure. There were no major imbalances between the 2 treatment groups within the moderate and less severe stroke groups.

### Efficacy Outcomes

Overall, the rate of the primary efficacy end point was greater in patients with moderate stroke compared with those with less severe stroke (7.6% [129 of 1671] vs 4.7% [158 of 3359] in the ticagrelor group; 9.1% [150 of 1641] vs 5.7% [190 of 3312] in the placebo group) (Table 2). No significant interaction between treatment assignment and NIHSS group for the pri-

**Table 2. Outcomes of Patients Receiving Ticagrelor or Placebo by Baseline National Institutes of Health Stroke Scale (NIHSS) Group**

Outcome	Ticagrelor (n = 5030)			Placebo (n = 4953)			Hazard ratio (95% CI)	P value	P value for interaction
	Total patients, No.	Events, No. (%)	Event rate (KM estimate), %	Total patients, No.	Events, No. (%)	Event rate (KM estimate), %			
<b>Primary efficacy end point</b>									
Stroke or death									
NIHSS score of 0-3	3359	158 (4.7)	4.7	3312	190 (5.7)	5.7	0.82 (0.66-1.01)	.06	.88
NIHSS score of 4-5	1671	129 (7.7)	7.6	1641	150 (9.1)	9.1	0.84 (0.66-1.06)	.14	
<b>Secondary efficacy end point</b>									
Ischemic stroke									
NIHSS score of 0-3	3359	143 (4.3)	4.2	3312	182 (5.5)	5.4	0.77 (0.62-0.96)	.02	.64
NIHSS score of 4-5	1671	121 (7.2)	7.2	1641	141 (8.6)	8.6	0.83 (0.65-1.06)	.14	
<b>Safety end points</b>									
GUSTO severe bleeding									
NIHSS score of 0-3	3359	16 (0.5)	0.5	3312	3 (0.1)	0.1	5.28 (1.54-18.10)	.008	.26
NIHSS score of 4-5	1671	8 (0.5)	0.5	1641	4 (0.2)	0.2	1.97 (0.59-6.53)	.27	
Intracranial hemorrhage or fatal bleeding									
NIHSS score of 0-3	3359	13 (0.4)	0.4	3312	3 (0.1)	0.1	4.29 (1.22-15.04)	.02	.41
NIHSS score of 4-5	1671	6 (0.4)	0.4	1641	3 (0.2)	0.2	1.97 (0.49-7.86)	.34	
Fatal bleeding									
NIHSS score of 0-3	3359	3 (0.1)	0.1	3312	1 (0.0)	0.0	2.96 (0.31-28.47)	.35	.75
NIHSS score of 4-5	1671	5 (0.3)	0.3	1641	1 (0.1)	0.1	4.91 (0.57-42.05)	.15	
Intracranial hemorrhage									
NIHSS score of 0-3	3359	13 (0.4)	0.4	3312	3 (0.1)	0.1	4.29 (1.22-15.04)	.02	.32
NIHSS score of 4-5	1671	5 (0.3)	0.3	1641	3 (0.2)	0.2	1.64 (0.39-6.86)	.50	
Hemorrhagic stroke									
NIHSS score of 0-3	3359	5 (0.1)	0.1	3312	2 (0.1)	0.1	2.47 (0.48-12.73)	.28	.99
NIHSS score of 4-5	1671	3 (0.2)	0.2	1641	0	NA	NA	NA	
GUSTO moderate or severe bleeding									
NIHSS score of 0-3	3359	20 (0.6)	0.6	3312	5 (0.2)	0.2	3.95 (1.48-10.54)	.006	.33
NIHSS score of 4-5	1671	12 (0.7)	0.7	1641	6 (0.4)	0.3	1.98 (0.74-5.28)	.17	
Premature permanent discontinuation of study drugs due to bleeding									
NIHSS score of 0-3	3359	90 (2.7)	2.9	3312	19 (0.6)	0.6	4.75 (2.89-7.79)	<.001	.79
NIHSS score of 4-5	1671	47 (2.8)	3.0	1641	11 (0.7)	0.7	4.24 (2.20-8.17)	<.001	

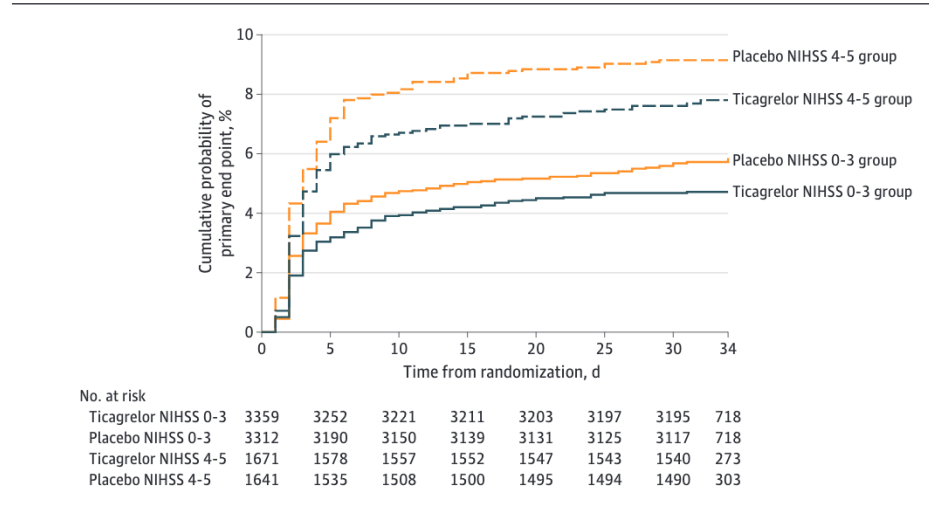
Abbreviations: GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; KM, Kaplan-Meier; NA, not applicable.

primary efficacy end point of stroke or death was identified (Table 2), indicating consistent efficacy of ticagrelor vs placebo among patients with stroke with a baseline NIHSS score of 4 to 5 and 0 to 3. In patients with moderate stroke, the observed primary end point event rate in patients taking ticagrelor was numerically lower than that in patients taking placebo (7.6% vs 9.1%; HR, 0.84; 95% CI, 0.66 to 1.06; risk difference, -1.54%; 95% CI, -3.43 to 0.35), with a number needed to treat of 65 to avoid 1 stroke or death at day 30 (Table 2). This effect size was similar to that in patients with less severe stroke (4.7% vs 5.7%; HR, 0.82; 95% CI, 0.66 to 1.01; risk difference, -1.00%; 95% CI, -2.06 to 0.06), with a number needed to treat of 100. Kaplan-Meier event curves for the primary efficacy end point by treatment assignment and baseline NIHSS group are shown in Figure 2. Ischemic stroke occurred in 121 patients (7.2%) in the ticagrelor group vs 141 patients (8.6%) in the placebo group among those with moderate stroke (HR, 0.83;

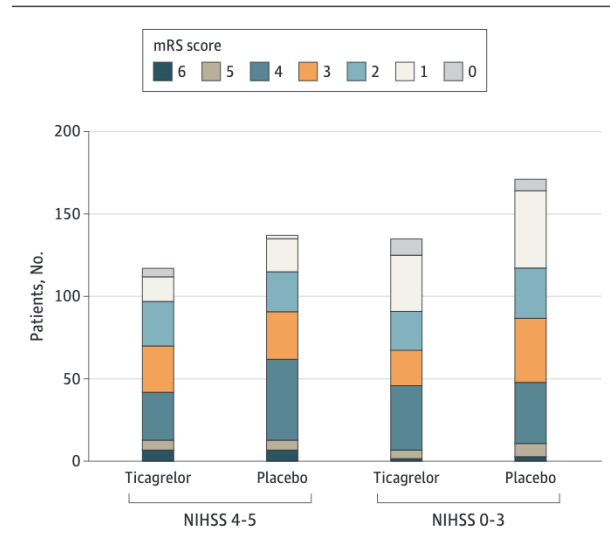
95% CI, 0.65 to 1.06), compared with 143 patients (4.3%) in the ticagrelor group vs 182 patients (5.5%) in the placebo group among those with less severe stroke (HR, 0.77; 95% CI, 0.62 to 0.96) (*P* for interaction = .64; Table 2). Similar findings were observed when the entire population regardless of qualifying event was included (eTable 2 and eFigure 1 in Supplement 2).

The proportion of overall disability (mRS score greater than 1) at day 30 was greater in patients with moderate stroke compared with those with less severe stroke (37.2% [612 of 1643] vs 18.8% [620 of 3299] in the ticagrelor group; 37.6% [609 of 1619] vs 19.4% [627 of 3236] in the placebo group; eTable 3 in Supplement 2). Efficacy of ticagrelor on overall disability at day 30 in patients with stroke with a baseline NIHSS score of 4 to 5 (37.2% vs 37.6%; OR, 0.98; 95% CI, 0.85 to 1.13) was similar to that in patients with a stroke with an NIHSS score of 0 to 3 (18.8% vs 19.4%; OR, 0.96; 95% CI, 0.85 to 1.09) (*P* for inter-

**Figure 2. Kaplan-Meier Event Curves for the Primary Efficacy End Point (Stroke or Death) by Treatment Assignment and Baseline National Institutes of Health Stroke Scale (NIHSS) Group**



**Figure 3. Modified Rankin Scale (mRS) Score Distribution at Day 30 in Patients With an Ischemic Stroke by Baseline National Institutes of Health Stroke Scale (NIHSS) Group**



action = .86). Distributions of mRS scores at day 30 with and without a subsequent ischemic stroke are shown in eTable 4 in Supplement 2. These data suggest a greater disability in patients with a subsequent stroke compared with those without a subsequent stroke. In patients with moderate stroke, a subsequent disabling stroke up to day 30 occurred in 99 of 1667 patients (5.9%) in the ticagrelor group and in 115 of 1637 patients (7.0%) in the placebo group (OR, 0.83; 95% CI, 0.63 to 1.10), with a number needed to treat of 91 to avoid 1 disabling stroke at day 30; the effect size was similar in those with less severe stroke (OR, 0.78; 95% CI, 0.59 to 1.03) (*P* for interaction = .74; Figure 3; eTable 3 in Supplement 2). Similar findings were observed when the entire population regardless of qualifying event was included (eTables 5 and eTable 6 and eFigure 2 in Supplement 2).

### Safety Outcomes

Among those with stroke with a baseline NIHSS score of 4 to 5, the primary safety end point, GUSTO severe bleeding, occurred in 8 patients (0.5%) in the ticagrelor group and in 4 patients (0.2%) in the placebo group (HR, 1.97; 95% CI, 0.59 to 6.53; risk difference, 0.24%; 95% CI, -0.18 to 0.65), with a number needed to harm of 425 to produce 1 severe bleeding within 30 days, while the primary safety end point in those with an NIHSS score of 0 to 3 occurred in 16 patients (0.5%) in the ticagrelor group and 3 patients (0.1%) in the placebo group (risk difference, 0.39%; 95% CI, 0.13 to 0.64), with a number needed to harm of 259 (*P* for interaction = .26) (Table 2). In patients with moderate stroke, GUSTO moderate or severe bleeding occurred in 12 patients (0.7%) in the ticagrelor group and in 6 patients (0.4%) in the placebo group (HR, 1.98; 95% CI, 0.74 to 5.28). Similar to that in patients with less severe stroke, permanent discontinuation of study drug in patients with moderate stroke was more common in the ticagrelor group than in the placebo group. Similar findings were observed when the entire population regardless of qualifying event was included (eTable 2 in Supplement 2).

### Discussion

In this exploratory analysis of the THALES trial, we found that although the risk of subsequent stroke or death was numerically higher in patients presenting with moderate ischemic stroke, the relative efficacy and safety of ticagrelor added to aspirin were similar to those presenting with less severe ischemic events. Ticagrelor plus aspirin treatment appears beneficial and safe in both the less severe and moderate stroke subgroups.

Prognosis and clinical management of patients with ischemic stroke of moderate severity has drawn physicians' attention in recent years. Consistent with our results, previous studies showed that patients with strokes of moderate severity have a higher risk of deterioration and poor outcome com-



pared with those with low severity.<sup>10,11</sup> The efficacy of DAPT with clopidogrel and aspirin in patients with high-risk TIA or minor ischemic stroke with a baseline NIHSS score of 0 to 3 was evaluated in the CHANCE and POINT trials.<sup>5,6</sup> Pooled analysis of the POINT and CHANCE trials demonstrated that 21-day clopidogrel plus aspirin therapy reduced the risk of major ischemic events at 90 days by 34% without any significant increase in major hemorrhages (0.1% vs 0.3%; nominal  $P = .10$ ) for patients with high-risk TIA or minor ischemic stroke with a baseline NIHSS score of 0 to 3.<sup>12</sup> Patients with stroke of higher severity may respond differently than patients with mild stroke severity to DAPT; however, to our knowledge, no clinical trials have evaluated the efficacy of DAPT in patients with stroke with an NIHSS score of 4 to 5. In addition, the risk of bleeding, especially severe bleedings events, such as intracranial hemorrhage, was the major concern when intensive antiplatelet therapy was administered for patients with moderate stroke in clinical practice.<sup>13</sup> Prior DAPT trials in patients with acute ischemic stroke have suggested an increase in minor extracranial bleedings with higher NIHSS scores, but this was not observed for intracranial hemorrhage.<sup>14,15</sup> The present study provided additional evidence that DAPT with ticagrelor and aspirin had consistent benefit and risk of severe bleeding events, such as intracranial hemorrhage, between patients with baseline NIHSS scores of 4 to 5 and those with baseline NIHSS scores of 0 to 3. Additionally, the absolute increase in risk of intracranial bleedings or other severe bleeding events for ticagrelor plus aspirin treatment was low (risk difference, 0.24%; 95% CI, -0.18 to 0.65), with a number needed to harm of 425 to produce 1 severe bleeding event within 30 days.

A major sequela of stroke is disability, which in turn is associated with poor long-term prognosis and health-related quality of life as well as high societal cost.<sup>16-18</sup> Although patients with minor stroke or TIA had mild and nondisabling symptoms, these patients have a high risk of new stroke during the short-term period (5% to 12% within 3 months), most of which are disabling.<sup>5,19,20</sup> Because of greater severity of the index stroke, patients with baseline NIHSS scores of 4 to 5 may have more overall disability and risk of developing disabling stroke than those with baseline NIHSS scores of 0 to 3.<sup>21-23</sup> However, even if there is a high risk of disability from the index

event, a subsequent stroke can have a substantial impact on outcomes. A previous secondary analysis of the THALES trial showed that ticagrelor plus aspirin treatment was superior to aspirin alone in preventing disabling stroke or death at 30 days and reduced the total burden of disability owing to ischemic stroke recurrence in the entire population of the trial.<sup>24</sup> The present study indicates that ticagrelor plus aspirin treatment prevents disabling stroke in the subgroups of patients presenting with minor and with moderate stroke. Given the high risk of new stroke and developing disabling stroke, intensive antiplatelet therapy should also be started as a matter of urgency to prevent new or worsening stroke events in patients with ischemic stroke with a baseline NIHSS score of 4 to 5.

### Limitations

This study has several limitations. This is an exploratory subgroup analysis of a large-scale randomized clinical trial, and type I errors can be introduced in such analyses. Although the THALES trial is the largest acute DAPT stroke trial to date, the number of patients with stroke with an NIHSS score of 4 to 5 was 3312 of 11 016 patients (30.1%), with modest power. Therefore, caution is warranted when interpreting the present findings, especially for the safety outcome due to the small number of bleeding events. Most patients with acute ischemic stroke present with an NIHSS score of 0 to 5<sup>25</sup>; however, the efficacy and safety of ticagrelor in patients with NIHSS scores greater than 5 has not been studied.

### Conclusions

The present exploratory analysis showed that patients with an acute ischemic stroke with a baseline NIHSS score of 4 to 5 have a consistent benefit from receiving treatment with ticagrelor plus aspirin vs aspirin alone as patients with baseline NIHSS score of 0 to 3, with no further increase in the risk of intracranial bleedings or other severe bleeding events. Although the risk of disability is higher overall in patients with stroke with a baseline NIHSS score of 4 to 5 owing to greater severity of the index event, DAPT with ticagrelor and aspirin reduced the number of patients with subsequent disabling stroke.

#### ARTICLE INFORMATION

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